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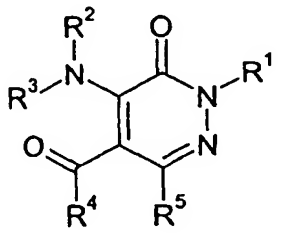
(54) Title: PYRIDAZIN-3(2*H*)-ONE DERIVATIVES AS PDE4 INHIBITORS



(I)

(57) Abstract: New pyridazin-3(2*H*)-one derivatives having the chemical structure of general formula (I); are disclosed; as well as processes for their preparation, pharmaceutical compositions comprising them and their use in therapy as inhibitors of phosphodiesterase 4.

PYRIDAZIN-3(2H)-ONE DERIVATIVES AS PDE4 INHIBITORS

This invention relates to new pyridazin-3(2*H*)-one derivatives, to processes for their preparation and to pharmaceutical compositions containing them. These compounds are potent and selective inhibitors of phosphodiesterase 4 (PDE4) and are thus useful in the treatment, prevention or suppression of pathological conditions, diseases and disorders known to be susceptible of being improved by inhibition of PDE4.

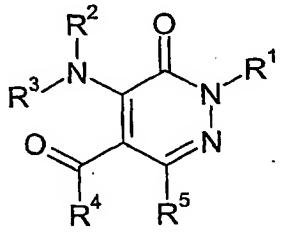
Phosphodiesterases (PDEs) comprise a superfamily of enzymes responsible for the hydrolysis and inactivation of the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Eleven different PDE families have been identified to date (PDE1 to PDE11) which differ in substrate preference, catalytic activity, sensitivity to endogenous activators and inhibitors, and encoding genes.

The PDE4 isoenzyme family exhibits a high affinity for cyclic AMP but has weak affinity for cyclic GMP. Increased cyclic AMP levels caused by PDE4 inhibition are associated with the suppression of cell activation in a wide range of inflammatory and immune cells, including lymphocytes, macrophages, basophils, neutrophils, and eosinophils. Moreover, PDE4 inhibition decreases the release of the cytokine Tumor Necrosis Factor α (TNFα). The biology of PDE4 is described in several recent reviews, for example M. D. Houslay, *Prog. Nucleic Acid Res. Mol. Biol.* **2001**, *69*, 249-315; J. E. Souness et al. *Immunopharmacol.* **2000** *47*, 127-162; or M. Conti and S. L. Jin, *Prog. Nucleic Acid Res. Mol. Biol.* **1999**, *63*, 1-38.

In view of these physiological effects, PDE4 inhibitors of varied chemical structures have been recentlty disclosed for the treatment or prevention of chronic and acute inflammatory diseases and of other pathological conditions, diseases and disorders known to be susceptible to amelioration by inhibition of PDE4. See, for example, US 5449686, US 5710170, WO 98/45268, WO 99/06404, WO 01/57025, WO 01/57036, WO 01/46184, WO 97/05105, WO 96/40636, US 5786354, US 5773467, US 5753666, US 5728712, US 5693659, US 5679696, US 5596013, US 5541219, US 5508300, US 5502072 or H. J. Dyke and J. G. Montana, *Exp. Opin. Invest. Drugs* **1999**, *8*, 1301-1325.

We have now found that a novel series of pyridazin-3(2*H*)-one derivatives are potent and selective inhibitors of PDE4 and are therefore useful in the treatment or prevention of these pathological conditions, diseases and disorders, in particular asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

Accordingly, the present invention provides novel compounds of formula (I)



(I)

wherein

R^1 represents:

- a hydrogen atom;
- a group selected from acyl, alkoxycarbonyl, carbamoyl, monoalkylcarbamoyl or dialkylcarbamoyl;
- an alkyl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, carbamoyl or mono- or di-alkylcarbamoyl groups;
- or a group of formula

$$-(CH_2)_n-R^6$$

wherein n is an integer from 0 to 4 and R^6 represents:

- a cycloalkyl group;
- an aryl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and alkyl, hydroxy, alkoxy, alkylenedioxy,

alkylthio, amino, mono- or di-alkylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, cyano, trifluoromethyl, difluoromethoxy or trifluoromethoxy groups;

- or a 3- to 7-membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and alkyl, hydroxy, alkoxy, alkylenedioxy, amino, mono- or di-alkylamino, nitro, cyano or trifluoromethyl groups;

R^2 represents a substituent selected from R^1 and an alkyl group, which is substitued by a hydroxycarbonyl or an alkoxycarbonyl group.

R^3 and R^5 each independently represent a monocyclic or bicyclic aryl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from:

- halogen atoms;
- alkyl and alkylene groups, which are optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and phenyl, hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl or mono- or di-alkylcarbamoyl groups;
- and phenyl, hydroxy, alkylenedioxy, alkoxy, cycloalkyloxy, alkylthio, alkylsulphinyl, amino, mono- or di-alkylamino, acylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido, alkylsulphamido, aminosuphonyl, mono- or di-alkylaminosulphonyl, cyano, difluoromethoxy or trifluoromethoxy groups;

R^4 represents:

- a hydrogen atom;
- a hydroxy, alkoxy, amino, mono- or di-alkylamino group;
- an alkyl group which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl and mono- or di-alkylcarbamoyl groups;
- or a group of formula

$-(CH_2)_n-R^6$

wherein n and R^6 are as defined above.

with the proviso that when R^2 is H and R^3 and R^5 are unsubstituted phenyl, R^1 is not methyl;

or a pharmaceutically acceptable salt thereof.

Certain pyridazin-3(2*H*)-one derivatives of similar structure, which do not fall within the scope of the present invention, have been disclosed in *J. Pharm. Sci.* **1991**, *80*, 341-348 and *J. Med. Chem.* **1999**, *42*, 1894-1900.

Further objectives of the present invention are to provide processes for preparing said compounds; pharmaceutical compositions comprising an effective amount of said compounds; the use of the compounds in the manufacture of a medicament for the treatment of diseases susceptible of being improved by inhibition of PDE4; and methods of treatment of diseases susceptible to amelioration by inhibition of PDE4, which methods comprise the administration of the compounds of the invention to a subject in need of treatment.

As used herein, an alkyl group can be straight or branched, and is typically a lower alkyl group. A lower alkyl group contains 1 to 6, preferably 1 to 4 carbon atoms. In particular it is preferred that such an alkyl group is represented by a methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, n-hexyl or 1-ethylbutyl group, .

As used herein, an alkylene group or moiety is a divalent alkyl moiety typically having from 1 to 6 carbon atoms. Examples of C_1-C_6 alkylene groups include methylene, ethylene, propylene, butylene, pentylene and hexylene groups. When an alkylene or alkylenedioxy group is present as a substituent on another group it shall be deemed to be a single substituent, rather than a group formed by two substituents.

As used herein, the alkyl chains present in the alkoxy, alkylthio, monoalkylamino, dialkylamino, alkoxycarbonyl, monoalkylcarbamoyl, dialkylcarbamoyl, alkylenedioxy,

alkylsulphinyl, monoalkylaminosulphonyl, dialkylaminosulphonyl, alkylsulphamido, N'-alkylureido, and N',N'-dialkylureido groups are typically straight or branched alkyl chains containing from 1 to 6 carbon atoms.

As used herein, an acyl group or moiety typically has from 2 to 7 carbon atoms. Thus, it is typically a group of formula -COR wherein R is a hydrocarbon chain group having from 1 to 6 carbon atoms. Preferably, it is a group of formula -COR wherein R is a C_1-C_6 alkyl group.

As used herein, a cycloalkyl group or moiety typically has from 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is preferably cyclopropyl, cyclopentyl or cyclohexyl. When a cycloalkyl group or moiety carries 2 or more substituents, the substituents may be the same or different. As used herein, a cycloalkyloxy group is typically a said cycloalkyl group attached to an oxygen atom.

As used herein, an aryl group or moiety is typically a C_6-C_{10} aryl group or moiety, which can be monocyclic or bicyclic, such as phenyl or naphthyl. When an aryl group or moiety carries 2 or more substituents, the substituents may be the same or different. As used herein, an aryloxy group is typically a said aryl group attached to an oxygen atom.

As used herein, a 3- to 7-membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur is typically a heteroaryl or a heterocyclyl group or moiety.

A heteroaryl group or moiety is typically a 3- to 7-membered aromatic ring, such as a 5- or 6- membered ring, containing at least one heteroatom selected from O, S and N. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, oxadiazolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, thienyl, pyrazolidinyl, pyrrolyl and pyrazolyl groups. Oxadiazolyl, oxazolyl, pyridyl, pyrrolyl, imidazolyl, thiazolyl, thiadiazolyl, furanyl, thienyl, pyrazinyl and pyrimidinyl groups are preferred. When a heteroaryl group or moiety carries 2 or more substituents, the substituents may be the same or different.

A heterocyclyl group is typically a non-aromatic, saturated or unsaturated C_3-C_7 carbocyclic ring in which one or more, for example 1, 2, 3 or 4, of the carbon atoms are replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl groups are

preferred. Examples of suitable heterocyclyl groups include piperidinyl, piperazinyl, morpholinyl, 4,5-dihydro-oxazolyl, 3-aza-tetrahydrofuranyl, imidazolidinyl and pyrrolidinyl groups. Where a heterocyclyl group carries 2 or more substituents, the substituents may be the same or different.

As used herein, a halogen atom, is typically a chlorine, fluorine or bromine atom.

As used herein, some of the atoms, groups, moieties, chains or cycles present in the general structures of the invention are "optionally substituted". This means that these atoms, groups, moieties, chains or cycles can be either unsubstituted or substituted by one or more, for example 1, 2, 3 or 4, substituents, whereby the hydrogen atoms bound to the unsubstituted atoms, groups, moieties, chains or cycles are replaced by chemically acceptable atoms, groups, moieties, chains or cycles.

Compounds of formula (I) containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic or nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, aralkyl amines and heterocyclic amines.

Preferred compounds of formula (I) are those wherein R^1 is a hydrogen atom; a straight or branched C_1-C_4 alkyl group, which is optionally substituted by halogen atoms and/or 1 or 2 substituents selected from hydroxy, alkoxy, amino, monalkylamino and dialkylamino groups; or a group of formula $-(CH_2)_n-R^6$, wherein n is an integer from 0 to 4 and R^6 is an optionally substituted phenyl, cycloalkyl or 5- to 6-membered heterocyclic ring comprising at least one nitrogen atom, preferably a pyridine ring. Most preferably, R^1 is an unsubstituted straight or branched C_1-C_4 alkyl group, or a group of formula $-(CH_2)_n-R^6$, wherein n is 0 or 1 and R^6 is cyclopropyl, phenyl or pyridyl.

Further preferred compounds of formula (I) are those wherein R^2 is a hydrogen atom or a group selected from alkoxycarbonyl; carbamoyl; a straight C_1-C_4 alkyl group, which is optionally substituted by a hydroxy group; or a group of formula $-(CH_2)_n-R^6$, wherein n is 0 and R^6 is a phenyl ring, which is optionally substituted by 1 or 2 substituents selected from halogen, alkyl, acyl, alkoxy, alkylthio and alkoxycarbonyl. Most preferably, R^2 is a hydrogen atom, an unsubstituted straight C_1-C_4 alkyl group or a phenyl ring, which is optionally substituted by 1 or 2 substituents selected from halogen, alkyl, acyl, alkoxy, alkylthio and alkoxycarbonyl.

Also preferred are compounds wherein R^3 is a phenyl or naphthyl group, which is optionally substituted by 1 or 2 substituents selected from halogen, hydroxy, alkoxy, cycloalkyloxy, alkylthio, cyano, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, acylamino, aminosulphonyl, carbamoyl, trifluoromethoxy, alkylenedioxy, alkyl and alkylene group, wherein said alkyl and alkylene groups are optionally substituted by halogen atoms or by a group selected from hydroxy, oxo, phenyl, amino and hydroxycarbonyl.

R^4 is in the preferred embodiments of the invention a substituent selected from hydrogen; hydroxy; alkoxy; amino; monoalkylamino; dialkylamino; a straight or branched C_1-C_6 alkyl group, which is optionally substituted by hydroxy, alkoxy, amino, monoalkylamino or dialkylamino groups; or a group of formula $-(CH_2)_n-R^6$, wherein n is 0, 1 or 2 and R^6 is a phenyl group. Most preferably, R^4 is a substituent selected from hydrogen, methoxy, unsubstituted straight or branched C_1-C_6 alkyl and phenyl.

In further preferred embodiments R^5 is a phenyl group, which is optionally substituted by 1 or 2 substituents selected from halogen, hydroxy, alkoxy, cycloalkyloxy, alkylthio, alkylsulphinyl, nitro, cyano, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, monalkylcarbamoyl, dialkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido and an optionally substituted straight or branched C_1-C_6 alkyl group. Most preferably, R^5 is a phenyl group, which is optionally substituted by 1 or 2 substituents selected from halogen, alkoxy, cycloalkyloxy, alkylthio, alkylsulphinyl and nitro.

Particular individual compounds of the invention include:

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3,5-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one.
5-Acetyl-2-ethyl-4-[(3-nitrophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(4-methylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(2-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-{[4-(methylthio)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(4-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-{[4-(dimethylamino)phenyl]amino}-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-(2-naphthylamino)-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-6-phenyl-4-([3-(trifluoromethoxy)phenyl]amino)pyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-6-phenyl-4-([2-(trifluoromethyl)phenyl]amino)pyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(2,5-dimethoxyphenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(2-fluoro-3-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(2,3-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(5-chloro-2-methoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(5-fluoro-2-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
Methyl 4-({5-acetyl-2-ethyl-6-[4-(methylthio)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoate
5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one
4-({5-Acetyl-2-ethyl-6-[4-(methylthio)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoic acid
5-Acetyl-2-ethyl-6-[4-(methylthio)phenyl]-4-(1-naphthylamino)pyridazin-3(2*H*)-one
5-Butyryl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one
2-Ethyl-5-(2-ethylbutanoyl)-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one
2-Ethyl-5-(2-ethylbutanoyl)-6-[4-(methylthio)phenyl]-4-(naphth-1-ylamino)pyridazin-3(2*H*)-one
Methyl 4-({5-acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-3-oxo-2,3-dihydropyrida-zin-4-yl}amino)benzoate
5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-(1-naphthylamino)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(3-nitrophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(2-methoxyphenyl)amino]pyridazin-3(2H)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(3-methoxyphenyl)amino]pyridazin-3(2H)-one

5-Acetyl-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-ethyl-4-(1-naphthylamino)pyridazin-3(2*H*)-one

5-Acetyl-2-methyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-benzyl-4-[(3,5-difluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-benzyl-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-benzyl-4-[(3-chlorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-(cyclopropylmethyl)-4-(1-naphthylamino)-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-(cyclopropylmethyl)-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-(1-naphthylamino)-6-phenyl-2-pyridin-4-ylmethylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-fluorophenyl)amino]-6-phenyl-2-pyridin-4-ylmethylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-methylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

2-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3,4-dimethoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-(1,1'-biphenyl-4-ylamino)-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-phenyl-4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)pyridazin-3(2*H*)-one

5-acetyl-4-{[3-(cyclopentyloxy)-4-methoxyphenyl]amino}-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[*N*-methyl-*N*-phenylamino]-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-(1,3-benzodioxol-5-ylamino)-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(4-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(4-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(4-bromophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-phenyl-4-{[3-(trifluoromethyl)phenyl]amino}pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chloro-4-methoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-hydroxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

5-Acetyl-2-ethyl-4-[(2-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

4-(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydro-pyridazin-4-ylamino)-benzoic acid ethyl ester

5-Acetyl-2-ethyl-4-[(4-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

2-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-4-fluorobenzoic acid

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-2-hydroxybenzoic acid

5-Acetyl-2-ethyl-4-[(3-hydroxy-4-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzamide

5-Acetyl-2-ethyl-4-{[3-(methylthio)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}acetic acid

5-Acetyl-4-[4-(*tert*-butylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzenesulphonamide

4-{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}-4-oxobutanoic acid

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-*N*-butylbenzenesulphonamide

5-Acetyl-2-ethyl-4-[(1-oxo-2,3-dihydro-1H-inden-5-yl)amino]-6-phenylpyridazin-3(2H)-one

N-{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}acetamide

4-[5-Acetyl-6-(3-chlorophenyl)-2-ethyl-3-oxo-2,3-dihydropyridazin-4-ylamino]benzoic acid

5-Acetyl-6-(3-chlorophenyl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2*H*)-one
5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one
5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(4-fluorophenyl)pyridazin-3(2*H*)-one
5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-(3-fluorophenyl)pyridazin-3(2H)-one
5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2*H*)-one
5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(3-nitrophenyl)pyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-(3-nitrophenyl)pyridazin-3(2H)-one
4-{[5-Acetyl-2-ethyl-6-(3-nitrophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzoic acid
5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-(3-nitrophenyl)pyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-(naphthalen-1-ylamino)-6-(3-nitrophenyl)pyridazin-3(2H)-one
5-Butyryl-4-[(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3-chlorophenyl)amino]-6-phenyl-2-propylpyridazin-3(2*H*)-one
5-Acetyl-2-butyl-4-[(3-chlorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3-bromophenyl)amino]-2-butyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[*N*-(3,5-dichlorophenyl)-*N*-(3-fluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[bis(3-fluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[bis(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[bis(3-methylsulphanylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[bis(3-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[bis-(3,5-dichlorophenyl)amino]-2-ethyl-6-phenyl-2*H*-pyridazin-3-one
methyl 4-{*N*-(5-acetyl-2-ethyl-6-(4-methylsulphinylphenyl)-3-oxo-2,3-dihydropyri-dazin-4-yl)-*N*-[4-(methoxycarbonyl)phenyl]amino}benzoate
5-Acetyl-2-(cyclopropylmethyl)-4-[(3,5-difluorophenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(3-fluorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2H)-one
4-[(5-Acetyl-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid
5-Acetyl-4-[(3,5-dichlorophenyl)amino]-2,6-diphenylpyridazin-3(2H)-one
5-Acetyl-4-[(3-fluorophenyl)amino]-2,6-diphenylpyridazin-3(2H)-one
5-Acetyl-4-(1-naphthylamino)-2,6-diphenylpyridazin-3(2H)-one
5-Acetyl-4-[(3,5-difluorophenyl)amino]-2,6-diphenylpyridazin-3(2H)-one
5-Acetyl-4-[(3-chlorophenyl)amino]-2,6-diphenylpyridazin-3(2H)-one
5-Benzoyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-methylpyridazin-3(2H)-one
5-[(3-Chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carbaldehyde

Methyl 5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

5-Acetyl-2-cyclobutyl-4-[(3,5-dichlorophenyl)amino]-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)(2-hydroxyethyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

4-[(3-Chlorophenyl)amino]-5-[(dimethylamino)acetyl]-2-ethyl-6-phenylpyridazin-3(2H)-one

4-{[2-Ethyl-5-(methoxyacetyl)-6-phenyl-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzoic acid

5-[(3-Cyanophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxamide

5-[(3-Cyanophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylic acid

3-{4-Acetyl-5-[(3,5-difluorophenyl)amino]-1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl}benzoic acid

3-{4-Acetyl-5-[(3,5-difluorophenyl)amino]-1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile

N-(3-{4-Acetyl-5-[(3,5-difluorophenyl)amino]-1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl}phenyl)urea

5-Acetyl-4-[(3-chlorophenyl)amino]-6-phenylpyridazin-3(2H)-one

N-Benzyl-5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxamide

4-[(3-Chlorophenyl)amino]-2-ethyl-5-(phenoxyacetyl)-6-phenylpyridazin-3(2H)-one

Of outstanding interest are:

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

4-({5-Acetyl-2-ethyl-6-[4-(methylthio)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoic acid

5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-(cyclopropylmethyl)-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

4-[5-Acetyl-6-(3-chlorophenyl)-2-ethyl-3-oxo-2,3-dihydropyridazin-4-ylamino]benzoic acid

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-(3-fluorophenyl)pyridazin-3(2*H*)-one

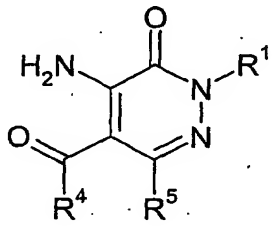
5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-(naphthalen-1-ylamino)-6-(3-nitrophenyl)pyridazin-3(2*H*)-one

5-Acetyl-2-(cyclopropylmethyl)-4-[(3,5-difluorophenyl)amino]-6-phenylpyridazin-3(2H)-one

In accordance with another embodiment, the present invention provides processes for preparing the novel pyridazin-3(2*H*)-one derivatives of formula (I). These compounds may be prepared following one of the processes described below.

When R^2 is H, the compounds of formula (I) are obtained by reaction of the corresponding 4-aminopyridazin-3(2*H*)-one derivative (II)



(II)

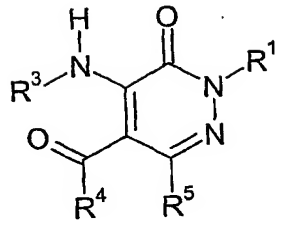
wherein R^1, R^4 and R^5 are as defined above and the corresponding boronic acid (IIIa)

R^3-$B(OH)_2$

(IIIa)

wherein R^3 is as defined above. The reaction is carried out in the presence of a copper salt such as cupric acetate and an organic base, preferably an amine base such as triethylamine, in an inert solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from - 20° C to the boiling point of the solvent.

When R^2 is aryl or substituted aryl, the compounds of formula (I) are obtained by reaction of the corresponding 4-aminopyridazin-3(2*H*)-one derivative (IV):



(IV)

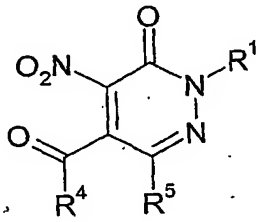
wherein R^1, R^3, R^4 and R^5 are as defined above and the corresponding boronic acid (IIIb)

R^2-$B(OH)_2$

(IIIb)

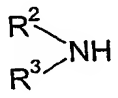
wherein R^2 is an aryl or substituted aryl group. The reaction is carried out in the presence of a copper salt such as cupric acetate and an organic base, preferably an amine base such as triethylamine, in an inert solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from - 20° C to the boiling point of the solvent.

Alternatively, the compounds of formula (I) may be obtained by reaction of the corresponding 4-nitropyridazin-3(2*H*)-one derivative (V):



(V)

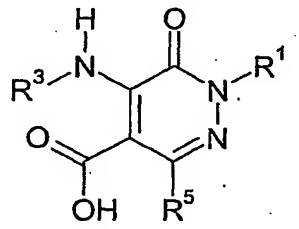
wherein R^1, R^4 and R^5 are as defined above and the corresponding amine (VI)



(VI)

wherein R^2 and R^3 are as defined above, by methods known per se, e. g. G. Ciciani et al. *Farmaco* **1991**, *46*, 873.

When R4 is alkoxy, aryloxy or mono- or di-alkylamino or mono- or di-arylamino, the compounds of formula (I) can be obtained by reaction of the corresponding 4-aminopyridazin-3(2H)-one derivative (XVII):

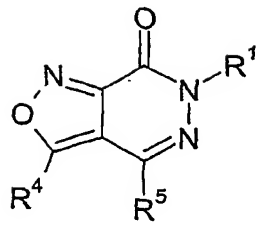


(XVII)

wherein R1, R3 and R5 are as defined above and the corresponding alcohol or amine in the presence of a coupling agent such as dicyclohexylcarbodiimide, O-7-(azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorofosfate (HATU) or benzotriazol-1-yloxytris-(dimethylamino)fosfonium hexafluorofosfate (BOP) in an inert solvent such as dichloromethane, tetrahydrofurane, dioxane, N,N-dimethylformamide and in the presence of an organic base such as triethylamine or ethyldiisopropylamine when required, at a temperature from –20°C to the boiling point of the solvent.

When R4 is alkoxy the compounds of formula (I) can also be obtained from the corresponding 4-aminopyridazin-3(2H)-one derivative (XVII) and the corresponding alkylating agent in the presence of an inorganic base such as potassium carbonate in an inert solvent such as N,N-dimethylformamide or acetone at a temperature from –20°C to the boiling point of the solvent.

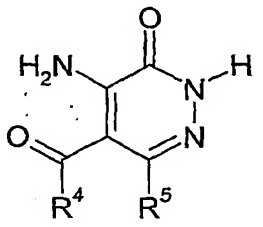
The 4-aminopyridazin-3(2*H*)-one derivatives of general formula (II) may be prepared by hydrogenation of an isoxazolo[3,4-*d*]pyridazin-7(6H)-one of formula (VII)



(VII)

wherein R^1, R^4 and R^5 are as defined above. The hydrogenation may be performed using for example hydrogen in the presence of a catalyst by methods known per se, e.g. V. Dal Piaz et al. *Heterocycles*, **1991**, *32*, 1173. Alternatively, the reaction may be accomplished by transfer hydrogenation using an organic hydrogen donor and a transfer agent, such as ammonium formate or hydrazine by methods known per se, e.g. V. Dal Piaz et al. *Heterocycles*, **1991**, *32*, 1173.

Alternatively, when R^1 is not H, the 4-aminopyridazin-3(2*H*)-one derivatives of formula (II) may be prepared by reaction of a compound of general formula (VIII)



(VIII)

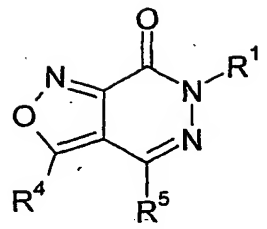
wherein R^4 and R^5 are as defined above, with an alkylating agent of formula (IX)

R^1-X

(IX)

wherein R^1 is as defined above and X is a leaving group such as a chlorine or a bromine atom or a methanesulphonate, p-toluenesulphonate or a benzenesulphonate group, by methods known per se, e. g. V. Dal Piaz et al. *Eur. J. Med. Chem.* **1996**, *31*, 65.

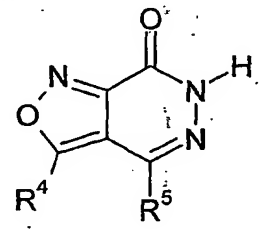
The 4-nitropyridazin-3(2*H*)-one derivatives of formula (V) may be prepared by oxidation of an isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one of formula (VII)



(VII)

wherein R^1, R^4 and R^5 are as defined above. The oxidation may be performed using for example cerium ammonium nitrate under acidic conditions by methods known per se, e.g. V. Dal Piaz et al. *Synthesis*, **1989**, 213.

When R^1 is not H, isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (VII) may be obtained by reaction of a compound of general formula (X)



(X)

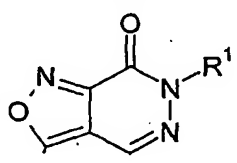
wherein R^4 and R^5 are as defined above with an alkylating agent of formula (IX)

R^1-X

(IX)

wherein R^1 is as hereinbefore defined and X is a leaving group such as a chlorine or a bromine atom or a methanesulphonate, p-toluenesulphonate or a benzenesulphonate group, by methods known per se, e.g. V. Dal Piaz et al. *Drug Des. Discovery* **1996**, *14*, 53.

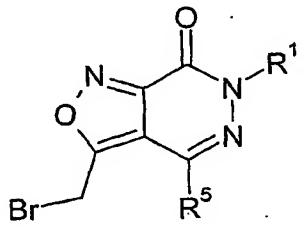
The 4-aminopyridazin-3(2*H*)-one derivatives of general formula (II) may alternatively be



obtained by reaction of a compound of formula (XVIII)

wherein R1 and R5 are as defined above with an aldehyde or a ketone, by methods known per se, eg. G. Ciciani et al. *Il Farmaco* **1991**, 46, 873. The resulting substituted vinyl derivative is then reduced using for example hydrogen in the presence of a catalyst such as palladium on charcoal in a solvent such as methanol, ethanol or ethyl acetate to yield the corresponding 4-aminopyridazin-3(2*H*)-one (II).

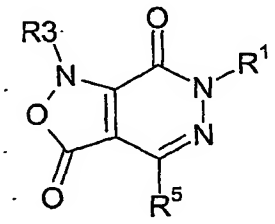
The isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (VII) can be obtained from a 3-(bromomethyl)isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one of formula (XIX)



(XIX)

by reaction with a nucleofile such as an alkoxide, an amine or a thiol by methods known per se, e.g. F. Montesano et al. *Bioorg. Med. Chem. Lett.* **1998**, *6*, 925.

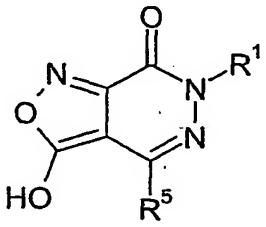
The 4-aminopyridazin-3(2H) one derivatives of general formula (XVII) may be prepared by hydrogenation of an isoxazolo[3,4-*d*]pyridazin-3,7-dione of formula (XX)



(XX)

wherein R^1 and R^5 are as defined above. The hydrogenation may be performed using for example hydrogen in the presence of a catalyst by methods known *per se*, e.g. V. Dal Piaz et al. *Heterocycles*, **1991**, *32*, 1173. Alternatively, the reaction may be accomplished by transfer hydrogenation using an organic hydrogen donor and a transfer agent, such as ammonium formate or hydrazine by methods known *per se*, e.g. V. Dal Piaz et al. *Heterocycles*, **1991**, *32*, 1173.

The isoxazolo[3,4-*d*]pyridazin-3,7-dione of formula (XX) may be obtained by reaction of the corresponding isoxazolo[3,4-*d*]pyridazin-7(*6H*)-one of formula (XXI)



(XXI)

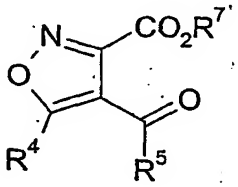
wherein R^1 and R^5 are as defined above and the corresponding boronic acid (IIIa)

R^3-$B(OH)_2$

(IIIa)

wherein R^3 is as defined above. The reaction is carried out in the presence of a copper salt such as cupric acetate and an organic base, preferably an amine base such as triethylamine, in an inert solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from - 20° C to the boiling point of the solvent.

The isoxazolo[3,4-*d*]pyridazin-7(*6H*)-ones of formulas (VII) and (XXI) may also be obtained alternatively by reaction of a compound of general formula (XI)



(XI)

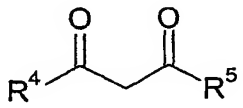
wherein R^4 and R^5 are as defined above and R^7 is an alkyl substituent with a hydrazine of general formula (XII)

R^1-$NHNH_2$

(XII)

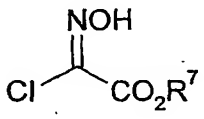
wherein R^1 is as defined above by methods known per se, e.g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, *95*, 1478.

The isoxazole derivatives of formula (XI) may be obtained by reaction of a 1,3-dicarbonylic compound of general formula (XIII)



(XIII)

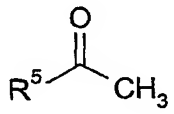
wherein R^4 and R^5 are as defined above and a compound of formula (XIV)



(XIV)

wherein R^7 is as defined above by methods known per se, e.g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, *95*, 1478.

The dicarbonylic compounds of formula (XIII) may be obtained by reaction of a methylketone of formula (XV)



(XV)

wherein R^5 is as defined above and an ester of formula (XVI)

$R^4CO_2R^8$

(XVI)

wherein R^8 is alkyl and R^4 is as defined above by methods known per se, e. g. V. V. Popic et al., *Synthesis* **1991**, 195.

When the defined groups R^1 to R^5 are susceptible to chemical reaction under the conditions of the hereinbefore described processes or are incompatible with said processes, conventional protecting groups may be used in accordance with standard practice, for example see T. W. Greene and P. G. M. Wuts in 'Protective Groups in Organic Chemistry', 3rd Edition, John Wiley & Sons (1999). It may be that deprotection will form the last step in the synthesis of compounds of formula (I).

The pharmaceutically acceptable salts of the compounds of the present invention represented by formula (I) may be acid addition salts or alkali addition salts. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, phosphate, diphosphate, and organic acid addition salts such as, for example, acetate, benzoate, maleate, fumarate, citrate, oxalate, ascorbate, succinate, tartrate, malate, mandelate, methanesulphonate, ethanesulphonate, benzenesulphonate and *p*-toluenesulphonate. Examples of the alkali addition salts include inorganic salts such as, for example sodium, potassium, calcium, magnesium and ammonium salts and organic alkali salts such as, for example, ethylenediamine, ethanolamine, *N,N*-dialkylenethanolamine, triethanolamine and basic amino acid salts.

The compounds of the present invention represented by the above described formula (I) may include enantiomers depending on their asymmetry or diastereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

PDE4 Assay Procedure

Compounds to be tested were resuspended in DMSO at a stock concentration of 1 mM. The compounds were tested at different concentrations varying from 10 µM to 10 pM to calculate an IC_{50}. These dilutions were done in 96-well plates. In some cases, plates containing diluted compounds were frozen before being assayed. In these cases, the plates were thawed at room temperature and stirred for 15 minutes.

Ten microliters of the diluted compounds were poured into a "low binding" assay plate. Eighty microliters of reaction mixture containing 50 mM Tris pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EGTA, and 15 nM [3H]-cAMP were added to each well. The reaction was initiated by

adding ten microliters of a solution containing PDE4. The plate was then incubated under stirring for 1 hour at room temperature. After incubation the reaction was stopped with 50 microlitres of SPA beads, and the reaction was allowed to incubate for another 20 minutes at room temperature before measuring radioactivity using standard instrumentation.

The reaction mixture was prepared by adding 90 ml of H_2O to 10 ml of 10X assay buffer (500 mM Tris pH 7.5, 83 mM $MgCl_2$, 17 mM EGTA), and 40 microlitres 1 μCi/μL [3H]-cAMP. SPA beads solution was prepared by adding 500 mg to 28 ml H_2O for a final concentration of 20 mg/ml beads and 18 mM zinc sulphate.

The results are shown in Table 1.

TABLE 1

Example	IC_{50} PDE4 (nM)
1	7.7
2	3.1
8	2
13	9.3
23	9.5
31	20
36	13
39	16
45	7.8
46	8.9
50	14
52	12
72	6.0
86	14
88	6.1
91	5.9
92	8.7
97	0.5
109	0.26

Example	IC_{50} PDE4 (nM)
120	7.1
176	19
181	25
190	9.3
231	20
232	13
263	15
264	11
274	5.5

The results in table 1 show that the compounds of formula (I) are potent inhibitors of phosphodiesterase 4 (PDE 4). Preferred pyridazin-3(2*H*)-one derivatives of the invention possess an IC_{50} value for the inhibition of PDE4 (determined as defined above) of less than 100 nM, preferably less than 50 nM and most preferably less than 20 nM. The compounds are also capable of blocking the production of some pro-inflammatory cytokines such as, for example, TNFα.

Thus, they can be used in the treatment of allergic, inflammatory and immunological diseases, as well as those diseases or conditions where the selective inhibition of PDE4 and the blockade of pro-inflammatory cytokines is known to be of benefit. These disease states include (see, for example, US 5449686, US 5710170, WO 98/45268, WO 99/06404, WO 01/57025, WO 01/57036, WO 01/46184, WO 97/05105, WO 96/40636, US 5786354, US 5773467, US 5753666, US 5728712, US 5693659, US 5679696, US 5596013, US 5541219, US 5508300, US 5502072 or H. J. Dyke and J. G. Montana, *Exp. Opin. Invest. Drugs* **1999**, *8*, 1301-1325) asthma, chronic obstructive pulmonary disease, allergic rhinitis, rheumatoid arthritis, osteoarthritis, osteoporosis, bone-formation disorders, glomerulonephritis, multiple sclerosis, ankylosing spondylitis, Graves ophtalmopathy, myasthenia gravis, diabetes insipidus, graft rejection, gastrointestinal disorders such as ulcerative colitis or Crohn disease, septic shock, adult distress respiratory syndrome, and skin diseases such as atopic dermatitis, contact dermatitis, acute dermatomyositis and psoriasis. They can also be used as improvers of cerebrovascular function as well as in the treatment of other CNS related diseases such as dementia, Alzheimer's disease, depression, and as nootropic agents.

The PDE4 inhibitors of the invention are also of benefit when administered in combination with other drugs such as steroids and immunosuppressive agents, such as cyclosporin A, rapamycin or T-cell receptor blockers. In this case the administration of the compounds allows a reduction of the dosage of the other drugs, thus preventing the appearance of the undesired side effects associated with both steroids and immunosuppressants.

Like other PDE4 inhibitors (see references above) the compounds of the invention can also be used for blocking the ulcerogenic effects induced by a variety of etiological agents, such as antiinflammatory drugs (steroidal or non-steroidal antiinflammatory agents), stress, ammonia, ethanol and concentrated acids. They can be used alone or in combination with antacids and/or antisecretory drugs in the preventive and/or curative treatment of gastrointestinal pathologies like drug-induced ulcers, peptic ulcers, H. Pylori-related ulcers, esophagitis and gastro-esophageal reflux disease.

They can also be used in the treatment of pathological situations where damage to the cells or tissues is produced through conditions like anoxia or the production of an excess of free radicals. Examples of such beneficial effects are the protection of cardiac tissue after coronary artery occlusion or the prolongation of cell and tissue viability when the compounds of the invention are added to preserving solutions intended for storage of transplant organs or fluids such as blood or sperm. They are also of benefit on tissue repair and wound healing.

Accordingly, another embodiment of he invention is the use of the pyridazin-3(2*H*)-one derivatives of formula (I) in the manufacture of a medicament for the treatment of pathological conditions or diseases susceptible to amelioration by inhibition of phosphodiesterase 4 (PDE4), as well as a method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by inhibition of PDE4, which comprises administering to said subject an effective amount of a compound of formula (I).

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a pyridazin-3(2*H*)-one derivative of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight, of the composition

depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, nasal, rectal, percutaneous or injectable administration.

The pharmaceutically acceptable excipients which are admixed with the active compound, or salts of such compound, to form the compositions of this invention are well-known per se and the actual excipients used depend inter alia on the intended method of administering the compositions.

Compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules, inhalation aerosols, inhalation solutions, dry powder inhalation, or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 2 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent and a flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid.

Compositions for topical administration may take the form of ointments, creams or lotions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

Effective doses are normally in the range of 10-600 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as a limiting.

^{1}H Nuclear Magnetic Resonance Spectra were recorded on a Varian Gemini 300 spectrometer. Low Resolution Mass Spectra (m/z) were recorded on a Micromass ZMD mass spectrometer using ESI ionization. Melting points were recorded using a Perkin Elmer DSC-7 apparatus. The chromatographic separations were obtained using a Waters 2690 system equipped with a Symmetry C18 (2.1 x 10 mm, 3.5 mM) column. The mobile phase was formic acid (0.4 ml), ammonia (0.1 ml), methanol (500 ml) and acetonitrile (500 ml) (B) and formic acid (0.46 ml), ammonia (0.115 ml) and water (1000 ml) (A): initially from 0% to 95% of B in 20 min, and then 4 min. with 95% of B. The reequilibration time between two injections was 5 min. The flow rate was 0.4 ml/min. The injection volume was 5 microliter. Diode array chromatograms were collected at 210 nM.

PREPARATION EXAMPLES

PREPARATION 1

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]butane-1,3-dione

To a stirred suspension of 60% sodium hydride (200 mg, 5 mmol) and ethyl acetate (0.49 ml, 5 mmol) in tetrahydrofuran (25 ml) were sequentially added a solution of 1-[3-(cyclopentyloxy)-4-methoxyphenyl]ethanone (European Patent Application EP470805) (590 mg, 2.5 mmol) in tetrahydrofuran (5 ml), two drops of ethanol and a solution of dibenzo-18-crown (15 mg, 0.04 mmol) in tetrahydrofuran (5 ml). The reaction mixture was refluxed for 5 h, allowed to cool to room temperature and finally quenched with aqueous 10% sulphuric acid solution (5 ml). The resulting mixture was diluted with diethyl ether, washed with saturated ammonium chloride solution, dried and concentrated under reduced pressure to yield a crude product which was purified by column chromatography (SiO2, hexane-ethyl acetate 4:1) to afford the title compound (610 mg, 86% yield) as a pale yellow oil.

$\delta(CDCl_3)$: 1.62 (m, 2H), 1.85 (m, 6H), 2.16 (s, 3H), 3.98 (s, 3H), 4.82 (m, 1H), 6.10 (s, 1H), 6.85 (d, 1H), 7.42 (m, 2H).

PREPARATION 2

Ethyl 5-methyl-4-[4-(methylthio)benzoyl]isoxazole-3-carboxylate.

To an ice-cooled solution of sodium ethoxide (3.2 g, 59 mmol) in absolute ethanol (125 ml) was added portionwise 1-[4-(methylthio)phenyl]butane-1,3-dione (Goerlitz, G., Hartmann, H. *Heteroat. Chem.*, **1997**, *8*, 147-55) (11.2 g, 54 mmol) and the mixture was stirred at 0° for 30 min. A solution of ethyl chloro(hydroximino)acetate (9.0 g, 59 mol) in absolute ethanol (25 ml) was added dropwise and the final mixture was stirred at room temperature overnight. The resulting mixture was acidified with acetic acid to pH 5-6 and concentrated. The residue thus obtained was partitioned between ethyl acetate and water, washed with brine, dried and concentrated under reduced pressure to yield the title compound (13.0 g , 70% yield) as a yellow solid.

$\delta(CDCl_3)$: 1.02 (t, 3H), 2.56 (s, 6H), 4.07 (q, 2H), 7.42 (d, 2H), 7.65 (d, 2H).

PREPARATION 3

Ethyl 4-[3-(cyclopentyloxy)-4-methoxybenzoyl]-5-methylisoxazole-3-carboxylate

Obtained as a yellow solid (91%) from 1-[3-(cyclopentyloxy)-4-methoxyphenyl]butane-1,3-dione (Preparation 1) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 2.

$\delta(CDCl_3)$: 1.02 (t, 3H),1.61 (m, 4H), 1.85 (m, 4H), 2.56 (s, 3H), 3.98 (s, 3H), 4.07 (q, 2H), 4.82 (m, 1H), 6.85 (d, 1H), 7.23 (d, 1H), 7.42 (s, 1H).

PREPARATION 4

Ethyl 4-(4-fluorobenzoyl)-5-methylisoxazole-3-carboxylate

Obtained (95%) from 1-(4-fluorophenyl)butane-1,3-dione (Joshi, K.C.; Pathak, V.N.; Garg, U. *J. Indian Chem. Soc.* **1983**, *60*, 1074-1076) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 2.

$\delta(CDCl_3)$: 1.1 (t, 3H), 2.50 (s, 3H), 4.20 (q, 2H), 7.20 (m, 2H), 7.80 (m, 2H).

PREPARATION 5

Ethyl 4-(3-fluorobenzoyl)-5-methylisoxazole-3-carboxylate

Obtained (79%) from 1-(3-fluorophenyl)butane-1,3-dione (Joshi, K.C.; Pathak, V.N.; Garg, U. *J. Indian Chem. Soc.* **1983**, *60*, 1074-1076) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 2.

$\delta(CDCl_3)$: 1.10 (t, 3H), 2.60 (s, 3H), 4.15 (q, 2H), 7.30 (m, 4H).

PREPARATION 6

Ethyl 4-benzoyl-5-propylisoxazole-3-carboxylate

Obtained (70%) from 1-phenylhexane-1,3-dione (Levine et al. *J. Amer. Chem. Soc.* **1945**, *67*, 1510) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 2.

$\delta(CDCl_3)$: 1.00 (t, 6H), 1.80 (m, 2H), 2.90 (t, 2H), 4.10 (q, 2H), 7.50 (m, 5H).

PREPARATION 7

3-Methyl-4-[4-(methylthio)phenyl]isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Hydrazine monohydrate (1.70 g, 35 mmol) was added dropwise to a solution of the title compound of Preparation 2 (7.11 g, 23 mmol) in dry ethanol (500 ml) and the resulting mixture was stirred overnight. After cooling with an ice bath, a precipitate was formed which was collected by filtration and washed with diethyl ether to yield the title compound (3.31 g, 53% yield) as a yellow solid.

$\delta(CDCl_3)$: 2.57 (s, 3H), 2.58 (s, 3H), 7.25 (d, 2H), 7.42 (d, 2H), 11.35 (bs, 1H).

PREPARATION 8

4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained as a yellow solid (93%) from the title compound of Preparation 3 using the experimental procedure described in Preparation 7.

$\delta(CDCl_3)$: 1.61-2.01 (m, 8H), 2.56 (s, 3H), 3.98 (s, 3H), 4.83 (m, 1H), 7.03 (m, 3H), 9.62 (bs, 1H).

PREPARATION 9

4-(4-Fluorophenyl)-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained (87%) from the title compound of Preparation 4, using the experimental procedure described in Preparation 7.

$\delta(CDCl_3)$: 2.55 (s, 3H), 7.30 (m, 2H), 7.60 (m,2H).

PREPARATION 10

4-(3-Fluorophenyl)-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one.

Obtained (81%) from the title compound of Preparation 5, following the experimental procedure described in Preparation 7.

δ($CDCl_3$): 2.60 (s, 3H), 7.3 (m, 4H), 9.90 (s, 1H).

PREPARATION 11

4-Phenyl-3-propylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained (40%) from the title compound of Preparation 6 following the experimental procedure described in Preparation 7.

δ($CDCl_3$): 0.90 (t, 3H), 1.80 (m, 2H), 2.80 (t, 2H), 7.50 (m, 5H), 10.0 (s, 1H).

PREPARATION 12

6-Ethyl-3-methyl-4-[4-(methylthio)phenyl]isoxazolo[3,4-d]pyridazin-7(6H)-one

Cesium carbonate (17.2 g, 53 mmol) was added to a solution of the title compound of Preparation 7 (2.4 g, 8.8 mmol) in dry dimethylformamide (30 ml) and the resulting suspension was stirred for 15 minutes. Then ethyl bromide (4.6 ml, 62 mmol) was added dropwise and the final mixture was stirred at room temperature overnight and then at 50°C for 5h. The mixture was concentrated and the residue thus obtained was suspended in ethyl acetate, washed with water and brine, dried and concentrated to yield the title compound (1.44 g, 54% yield) as a yellow solid.

δ($CDCl_3$): 1.38 (t, 3H), 2.57 (s, 3H), 2.58 (s, 3H), 4.23 (q, 2H), 7.35 (d, 2H), 7.48 (d, 2H).

PREPARATION 13

6-Ethyl-4-[4-(methylthio)phenyl]-3-propylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

To a stirred solution of the title compound of Preparation 7 (1.5 g , 5.4 mmol) in dry dimethylformamide (10 ml) was added a solution of sodium hydroxyde (0.43 g, 10.8 mmol) in dry dimethylformamide (5 ml) and the resulting mixture was stirred for 15 minutes. Then ethyl bromide (1.21 ml, 16.2 mmol) was added dropwise and the final mixture was stirred at room temperature for 2h, poured onto dichloromethane and washed with water and brine. The organic layer was dried and the solvent removed to yield a crude product that was purified by flash column chromatography (SiO_2, hexane-ethyl ether 4:1) to afford the title compound (0.20 g, 12% yield).

δ($CDCl_3$): 0.82 (t, 3H), 1.39 (t, 3H), 1.68(m, 2H), 2.57 (s, 3H), 2.82 (t, 2H), 4.23 (q, 2H), 7.35 (d, 2H), 7.42 (d, 2H).

PREPARATION 14

6-Ethyl-3-(1-ethylpropyl)-4-[4-(methylthio)phenyl]isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained as a subproduct (7%) in Preparation 13.

δ($CDCl_3$): 0.62 (t, 6H), 1.39 (t, 3H), 1.75(m, 4H), 2.59 (s, 3H), 2.78 (m, 1H), 4.24 (q, 2H), 7.38 (m, 4H).

PREPARATION 15

6-Ethyl-3-methyl-4-[4-(methylsulphinyl)phenyl]isoxazolo[3,4-d]pyridazin-7(6H)-one.

To an ice cooled stirred solution of the title compound of Preparation 12 (1.0 g, 3.32 mmol) in methanol (8 ml) was added dropwise a solution of sodium periodate (0.71 g, 3.35 mmol) in water (8 ml). The resulting mixture was stirred at 0°C for 2 h and then at room temperature overnight. The solvent was removed and the resulting slurry was suspended in water and extracted with ethyl acetate. The organic layer was dried and the solvent removed to yield the title product (0.70 g, 66%) as a pale yellow solid.

δ($CDCl_3$): 1.42 (t, 3H), 2.57 (s, 3H), 2.81 (s, 3H), 4.30 (q, 2H), 7.75 (d, 2H), 7.85 (d, 2H).

PREPARATION 16

4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6-ethyl-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained (38%) from the title compound of Preparation 8 following the experimental procedure described in Preparation 12.

δ($CDCl_3$): 1.42 (t, 3H), 1.61 (m, 2H), 1.91 (m, 6H), 2.58 (s, 3H), 3.98 (s, 3H), 4.17 (q, 2H), 4.83 (m, 1H), 7.03 (m, 3H).

PREPARATION 17

6-Ethyl-4-(4-fluorophenyl)-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

To a suspension of the title compound of Preparation 9 (0.49 g, 2.0 mmol) and anhydrous potassium carbonate (0.55 g, 4.0 mmol) in dry dimethylformamide (5.3 ml) was added ethyl bromide (0.44 g, 4.0 mmol) and the resulting mixture heated at 110°C for 40 minutes. Then ice-water was added (30 ml) and the resulting precipitate collected by filtration to afford the title compound (0.47 g, 86%) as a yellow solid.

δ($CDCl_3$): 1.40 (t, 3H), 2.58 (s, 3H), 4.23 (q, 2H), 7.20 (m,2H), 7.58 (m,2H).

PREPARATION 18

6-Ethyl-4-(3-fluorophenyl)-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained (84%) from the title compound from Preparation 10 following the experimental procedure described in Preparation 17.

$\delta(CDCl_3)$: 1.40 (t, 3H), 2.58 (s, 3H), 4.30 (q, 2H), 7.30 (m, 3H), 7.50 (m, 1H).

PREPARATION 19

6-Ethyl-4-phenyl-3-propylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained (90%) from the title compound from Preparation 11 following the experimental procedure described in Preparation 17.

$\delta(CDCl_3)$: 0.90 (t, 3H), 1.50 (t, 3H), 1.80 (m, 2H), 2.80 (m, 2H), 4.25 (m, 2H), 7.50 (s, 5H).

PREPARATION 20

6-(Cyclopropylmethyl)-3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained as a light brown solid (70%) from 3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (Renzi, G.; Pinzauti, S., *Il Farmaco Ed. Sci.* **1969**, *24*, 885-889) and cyclopropylmethyl bromide following the experimental procedure described in Preparation 17.

$\delta(CDCl_3)$: 0.42 (m, 4H), 1.38 (m, 1H), 2.55 (s, 3H), 4.08 (d, 2H), 7.61 (m, 5H).

PREPARATION 21

3-Methyl-4-phenyl-6-(pyridin-4-ylmethyl)isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

To a stirred suspension of 3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (1.5 g, 6.6 mmol) (Renzi, G.; Pinzauti, S., *Il Farmaco Ed. Sci.* **1969**, *24*, 885-889), 60% sodium hydride (0.63 g, 15.8 mmol) was added portionwise and the mixture stirred for 15 minutes. Then 4-(chloromethyl)pyridine hydrochloride (1.3g, 7.9 mmol) was added portionwise and the final mixture was stirred at 50°C for 7 h, then poured onto water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated in vacuo to yield a crude product that was crystallized from from isopropyl ether/petroleum ether to yield the title compound (1.66 g, 79% yield) as a light brown solid.

$\delta(CDCl_3)$: 2.55 (s, 3H), 5.38 (s, 2H), 7.38 (d, 2H), 7.57 (m, 5H), 8.58 (m, 2H).

PREPARATION 22

5-Acetyl-4-amino-2-ethyl-6-phenylpyridazin-3(2*H*)-one

A mixture of 6-ethyl-3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) (2.0 g, 7.83 mmol) and 10% palladium on charcoal (400 mg) in ethanol (400 ml) was shaken under hydrogen at room temperature and 2 bar for 3 h. The catalyst was filtered off and the solvent was removed under reduced pressure to yield the title compound (1.97 g, 98% yield).

m.p. 150.8-152.7°C

δ($CDCl_3$): 1.43 (t, 3H), 1.67 (bs, 2H), 1.78 (s, 3H), 4.26 (q, 2H), 7.45 (s, 5H).

PREPARATION 23

5-Acetyl-4-amino-2-ethyl-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one

A mixture of the title compound of Preparation 12 (0.5 g, 1.66 mmol) , 10% palladium on charcoal (106 mg) and ammonium formate (2.3 g, 39 mmol) in ethanol (20 ml) was refluxed overnight. An extra amount of catalyst (213 mg) was added and the mixture was refluxed for another 24 h. Finally, the catalyst was filtered off and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, dichloromethane) to yield the title compound (190 mg, 37%).

δ($CDCl_3$): 1.42 (t, 3H), 1.81 (s, 3H), 2.50 (s, 3H), 4.24 (q, 2H), 7.35 (m, 4H).

PREPARATION 24

4-Amino-5-butyryl-2-ethyl-6-[4-(methylthio)phenyl]pyridazin -3(2*H*)-one

Obtained (27%) from the title product of Preparation 13 following the procedure described in Preparation 23.

δ($CDCl_3$): 0.65 (t, 3H), 1.39 (m, 5H), 2.02 (t, 2H), 2.50 (s, 3H), 4.23 (q, 2H), 7.12 (bs, 2H), 7.35 (m, 4H).

PREPARATION 25

4-Amino-2-ethyl-5-(2-ethylbutanoyl)-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one

Obtained (56%) from the title product of Preparation 14 following the procedure described in Preparation 23.

δ($CDCl_3$): 0.52 (t, 6H), 1.35 (m, 7H), 2.10 (m, 1H), 2.51 (s, 3H), 4.24 (q, 2H), 7.01 (bs, 2H), 7.38 (m, 4H).

PREPARATION 26

5-Acetyl-4-amino-2-ethyl-6-[4-(methylsulphinyl) phenyl]pyridazin-3(2*H*)-one

Obtained (70%) from the title product of Preparation 15 following the procedure described in Preparation 23.

δ($CDCl_3$): 1.41 (t, 3H), 1.80 (s, 3H), 2.77 (s, 3H), 4.30 (q, 2H), 7.65 (d, 2H), 7.77 (d, 2H).

PREPARATION 27

5-Acetyl-4-amino-6-(3-cyclopentyloxy-4-methoxy-phenyl)-2-ethylpyridazin-3(2*H*)-one

Obtained (40%) from the title product of Preparation 16 following the procedure described in Preparation 23.

δ($CDCl_3$): 1.42 (t, 3H), 1.61-2.01 (m, 11H), 3.98 (s, 3H), 4.23 (q, 2H), 4.83 (m, 1H), 6.98 (m, 3H), 7.32 (bs, 2H).

PREPARATION 28

5-Acetyl-4-amino-2-benzyl-6-phenylpyridazin-3(2*H*)-one

Obtained (92%) from 6-benzyl-3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (Dal Piaz, V.; Ciciani, G.; Giovannoni, MP, *Farmaco*, **1991**, *46*, 435-47) following the procedure described in Preparation 23.

δ($CDCl_3$): 1.78 (s, 3H), 5.38 (s, 2H), 7.21-7.55 (m, 10H).

PREPARATION 29

5-Acetyl-4-amino-2-(cyclopropylmethyl)-6-phenylpyridazin-3(2*H*)-one

Obtained (90%) from the title compound of Preparation 20 following the procedure described in Preparation 23.

δ($CDCl_3$): 0.51 (m, 4H), 1.40 (m, 1H), 1.78 (s, 3H), 4.02 (d, 2H), 7.43 (m, 5H).

PREPARATION 30

5-Acetyl-4-amino-6-phenyl-2-(pyridin-4-ylmethyl) pyridazin-3(2*H*)-one

Obtained (85%) from the title compound of Preparation 21 following the procedure described in Preparation 23.

δ($CDCl_3$): 1.77 (s, 3H), 5.36 (s, 2H), 7.27 (d, 2H), 7.43 (m, 5H), 8.59 (d, 2H).

PREPARATION 31

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-nitropyridazin-3(2*H*)-one

To a stirred suspension of the title compound of Preparation 17 (0.5 g, 1.83 mmol) in a mixture of acetic acid (7.3 ml), water (7.3 ml) and nitric acid (2.5 ml), cerium ammonium

nitrate (6.0 g, 11 mmol) was added portionwise during 40 min. Addition of ice-cold water gave a crude precipitate which was filtered and washed with cold water to yield the title product (45% yield).

δ($CDCl_3$): 1.43 (t, 3H), 2.20 (s, 3H), 4.40 (q, 2H), 7.20 (m, 2H), 7.48 (m, 2H).

PREPARATION 32

5-Acetyl-2-ethyl-6-(3-fluorophenyl)-4-nitropyridazin-3(2*H*)-one

Obtained (40%) from the title product of Preparation 18 following the experimental procedure described in Preparation 31.

δ($CDCl_3$): 1.50 (t, 3H), 2.20 (s, 3H), 4.40 (q, 2H), 7.20 (m, 3H), 7.46 (m, 1H).

PREPARATION 33

5-Butyryl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one

Obtained (51%) from the title compound of Preparation 19 following the experimental procedure described in Preparation 31.

δ($CDCl_3$): 0.90 (t, 3H), 1.50 (m, 5H), 2.35 (m, 2H), 4.40 (q, 2H), 7.50 (m, 5H).

PREPARATION 34

6-Ethyl-3,4-diphenylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained as solid (91%) from 3,4-diphenylisoxazolo[3,4-d]pyridazin-7(6H)-one (Renzi, G.; Dal Piaz, *Gazz. Chim. It.* **1965**, *95*, 1478-91) and ethyl bromide following the experimental procedure described in Preparation 17.

δ($CDCl_3$): 1.40 (t, 3H), 4.38 (q, 2H), 7.35 (m, 10H).

PREPARATION 35

4-Amino-5-benzoyl-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained (90%) from the title product of Preparation 34 following the procedure described in Preparation 22.

δ($CDCl_3$): 1.43 (t, 3H), 4.38 (q, 2H), 6.88 (s, 2H), 7.10 (m, 4H), 7.24 (m, 3H), 7.43 (m, 3H).

PREPARATION 36

5-Amino-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carbaldehyde

A mixture of 5-amino-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carbaldehyde one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., *Heterocycles*, 1991, 32, 1173-9) (258 mg, 1.2 mmol),

ethyl bromide (294 mg, 2.7 mmol) and anhydrous potassium carbonate (240 mg, 2.4 mmol) in anhydrous DMF (5 mL) was stirred at 90° C for 2 h. Cold water (25 ml) was added and the precipitate was collected by filtration to yield the title product (88%).

δ($CDCl_3$): 1.43 (t, 3H), 4.27 (m, 2H), 6.95 (s, 2H), 7.48 (m, 5H), 9.75 (s, 1H).

PREPARATION 37

Ethyl 4-benzoyl-5-hydroxyisoxazole-3-carboxylate

To a cooled and stirred solution of sodium ethoxide, obtained from sodium (2.3g, 0.1 mol) and anhydrous EtOH (60 ml), a solution of ethyl benzoylacetate (9.6g, 0.05 mol) in the same solvent (5 ml) was slowly added. A solution of ethylcloro(hydroximino)acetate (7.55g, 0.05 mol) in anhydrous EtOH (10 ml) was added in a dropwise manner (over 1h period). The mixture was neutralized with 6N HCl and the alcoholic layer was evaporated. After dilution with cold water (150-200 mL), the suspension was extracted with ethyl ether and the aqueous layer was acidified with 6N HCl to afford the product which was recovered by filtration (45% yield).

δ(DMSO-d6): 1.25 (t, 3H), 4.15 (q, 2H), 7.50 (m, 3H), 7.80 (m, 2H), 10.80 (s, 1H).

PREPARATION 38

Methyl 5-amino-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

A mixture of the title compound of preparation 37 (200 mg, 0.76 mmol), hydrazine hydrate (165 mg, 3.3 mmol), PPA (12 g) and 12 mL anhydrous EtOH is stirred at 40° for 12 h. After dilution with water (40 ml) the crude precipitate was recovered by suction. Then it was suspended in 2mL of EtOH and ammonium formate (75 mg, 1.2 mmol) and 10% Pd/C (15 mg) were added. The mixture was refluxed for 1 h. Filtration and evaporation of the solvent yielded a product that was solved in anhydrous DMF (1.7 mL). Anhydrous potassium carbonate (50 mg, 0.5 mmol) and iodomethane (200 mg, 1.4 mmol) were added and the mixture was stirred at room temperature for 45 min. Cold water (20 ml) was then added and the title compound was collected by filtration (50% yield).

δ(CDCl3): 3.49 (s, 3H), 7.02 (s, 2H), 7.38 (s, 5H).

PREPARATION 39

Methyl 5-amino-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

To a mixture of the title compound of preparation 38 (122 mg, 0.5 mmol) and anhydrous potassium carbonate (140 mg, 1.4 mmol) in anhydrous DMF (1.4 mL) ethyl bromide (0.1

mL, 1.2 mmol) was added and it was refluxed under stirring for 1 h. The suspension was then diluted with cold water and the title product was collected by filtration (75% yield).

$\delta(CDCl_3)$: 1.41 (t, 3H), 3.48 (s, 3H), 4.25 (q, 2H), 7.00 (s, 2H), 7.38 (s, 5H).

PREPARATION 40

6-Ethyl-4-phenyl-3-styryl-6H-isoxazolo[3,4-d]pyridazin-7-one

To a freshly prepared solution of sodium methoxide (108 mg, 1.96 mmol) in methanol (2 mL), a solution of 6-ethyl-3-methyl-4-phenyl-6H-isoxazolo[3,4-d]pyridazin-7-one(500 mg, 1.96 mmol) (Dal Piaz, V.; Giovannoni, M.P.; Castellana, C.; *et al* ,J. Med. Chem. **1997**, *40*, 1417-1421) in 2 mL of dry methanol was added and the mixture was stirred for a while. Then, benzaldehyde (0.40 mL, 3.92 mmol) was added dropwise and the final mixture was refluxed for 2 hours. The resulting suspension was let to cool down and the final product (514 mg, 76% yield) was collected by filtration.

$\delta(CDCl_3)$: 1.40 (t, 3H), 4.31 (q, 2H), 6.80 (d, 1H), 7.35 (m, 5H), 7.68 (m, 6H).

PREPARATION 41

6-Ethyl-4-phenyl-3-(2-thiophen-3-yl-vinyl)-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained (75%) from 6-ethyl-3-methyl-4-phenyl-6H-isoxazolo[3,4-d]pyridazin-7-one (500 mg, 1.96 mmol) (Dal Piaz, V.; Giovannoni, M.P.; Castellana, C.; *et al* ,J. Med. Chem. **1997**, *40*, 1417-1421) and thiophene-3-carbaldehyde following the procedure described in Preparation 40.

$\delta(CDCl_3)$: 1.42 (t, 3H), 4.30 (q, 2H), 6.58 (d, 1H), 6.98 (d, 1H), 7.28 (m, 1H), 7.42 (m, 1H), 7.63 (m, 6H).

PREPARATION 42

6-Ethyl-4-phenyl-3-(2-pyridin-3-yl-vinyl)-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained (70%) from 6-ethyl-3-methyl-4-phenyl-6H-isoxazolo[3,4-d]pyridazin-7-one (500 mg, 1.96 mmol) (Dal Piaz, V.; Giovannoni, M.P.; Castellana, C.; *et al* ,J. Med. Chem. **1997**, *40*, 1417-1421) and pyridine-3-carbaldehyde following the procedure described in Preparation 40.

$\delta(CDCl_3)$: 1.41 (t, 3H), 4.30 (q, 2H), 6.80 (s, 1H), 6.88 (s, 1H), 7.50-7.66 (m, 7H), 8.60 (s, 2H).

PREPARATION 43

4-Amino-2-ethyl-6-phenyl-5-(3-phenylpropionyl)pyridazin-3(2H)-one

A mixture of the title compound of preparation 40 (514 mg, 1.50 mmol) and 10% palladium on charcoal (100 mg) in ethanol (100 ml) was shaken under hydrogen at room temperature and 2 bar overnight. The catalyst was filtered off and the solvent was removed under reduced pressure to yield the title compound (487 mg, 95% yield).

m.p. 115.1-116.1°C

$\delta(CDCl_3)$: 1.40 (t, 3H), 2.28 (t, 2H), 2.68 (t, 2H), 4.25 (q, 2H), 6.78 (m, 2H), 7.05 (m, 3H), 7.45 (m, 5H).

PREPARATION 44

4-Amino-2-ethyl-6-phenyl-5-(3-thien-3-ylpropanoyl)pyridazin-3(2H)-one Obtained (67%) from the title compound of Preparation 41 following the procedure described in Preparation 43.

$\delta(CDCl_3)$: 1.41 (t, 3H), 2.30 (t, 2H), 2.70 (t, 2H), 4.25 (q, 2H), 6.08 (d, 1H), 6.54-6.62 (m, 2H), 7.08-7.58 (m, 7H).

PREPARATION 45

4-Amino-2-ethyl-6-phenyl-5-(3-pyridin-3-yl-propanoyl)pyridazin-3(2H)-one Obtained (97%) from the title compound of Preparation 42 following the procedure described in Preparation 43.

$\delta(CDCl_3)$: 1.41 (t, 3H), 2.29 (t, 2H), 2.70 (t, 2H), 4.25 (q, 2H), 7.05-7.57 (m, 9H).

PREPARATION 46

6-Isopropyl-3-methyl-4-phenyl-6H-isoxazolo[3,4-d]pyridazin-7-one

To a stirred solution of 3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (0.5 g, 2.2 mmol) (Renzi, G.; Pinzauti, S., *Il Farmaco Ed. Sci.* **1969**, *24*, 885-889), triphenylphosphine (0.577 g, 2.2 mmol) and isopropanol (0.170 mL, 2.2 mmol) in 7 mL of dry THF, diethylazadicarboxilate (0.345 mL, 2.2 eq) was added dropwise and the resulting mixture was stirred at room temperature overnight. Then, solvent was removed and the crude product was purified by flash column cromathography (SiO_2, hexane-ethyl acetate) to yield the title product (374 mg, 63% yield).

$\delta(CDCl_3)$: 1.42 (d, 6H), 2.58 (s, 3H), 5.40 (m, 1H), 7.55 (m, 5H).

PREPARATION 47

5-Acetyl-4-amino-2-isopropyl-6-phenylpyridazin-3(2H)-one

Obtained (92%) from the title product of Preparation 46 following the procedure described in Preparation 23.

δ($CDCl_3$): 1.40 (d, 6H), 1.78 (s, 3H), 5.32 (m, 1H), 7.45 (m, 5H).

PREPARATION 48

6-(2-Hydroxyethyl)-3-methyl-4-phenyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (98%) from 3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (Renzi, G.; Pinzauti, S., *Il Farmaco Ed. Sci.* **1969**, *24*, 885-889) and 2-bromoethanol following the experimental procedure described in Preparation 17. The mixture was stirred at 50°C for 5h and the product was isolated by pouring the reaction mixture onto water and extracting with ethyl acetate.

δ(DMSO-d_6): 2.57 (s, 3H), 3.75 (q, 2H), 4.18 (t, 2H), 4.83 (t, 1H), 7.18 (m, 3H), 7.25 (m, 2H).

PREPARATION 49

5-Acetyl-4-amino-2-(2-hydroxyethyl)-6-phenylpyridazin-3(2H)-one

Obtained as a solid (99%) from the title compound of Preparation 48 following the procedure described in preparation 22.

δ(DMSO-d_6): 1.78 (s, 3H), 3.72 (t, 2H), 4.18 (t, 2H), 7.40 (m, 5H), 7.78 (bs, 2H).

PREPARATION 50

4-(3-Fluorophenyl)-6-(2-hydroxyethyl)-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (75%) from the title compound of Preparation 10 and 2-bromoethanol following the experimental procedure described in Preparation 17. The mixture was stirred at roo temperature overnight and the product was isolated by pouring the reaction mixture onto water and extracting with ethyl ether.

LRMS: m/Z 290 $(M+1)^+$

PREPARATION 51

5-Acetyl-4-amino-6-(3-fluorophenyl)-2-(2-hydroxyethyl)-2H-pyridazin-3-one

Obtained as a solid (86%) from the title compound of Preparation 50 following the procedure described in Preparation 22.

LRMS: m/Z 292 $(M+1)^+$

PREPARATION 52

4-(3-Chlorophenyl)-6-(cyclopropylmethyl)-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (67%) from 4-(3-chlorophenyl)-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) and cyclopropylmethyl bromide following the experimental procedure described in Preparation 17. The product was purified by column chromatography.

LRMS: m/z 316 $(M+1)^+$.

PREPARATION 53

5-Acetyl-6-(3-chlorophenyl)-2-(cyclopropylmethyl)-4-nitropyridazin-3(2H)-one

Obtained (21%) from the title product of Preparation 52 following the experimental procedure described in Preparation 31. The product was purified by column chromatography.

LRMS: m/z 348 $(M+1)^+$.

PREPARATION 54

6-(Cyclopropylmethyl)-4-(3-fluorophenyl)-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (37%) from the title compound from Preparation 10 and cyclopropylmethyl bromide following the experimental procedure described in Preparation 17. The product was purified by column chromatography.

$\delta(CDCl_3)$: 0.52 (m, 4H), 1.38 (m, 1H), 2.58 (s, 3H), 4.07 (d, 2H), 7.30 (m, 3H), 7.55 (m, 1H).

PREPARATION 55

5-Acetyl-2-(cyclopropylmethyl)-6-(3-fluorophenyl)-4-nitropyridazin-3(2H)-one

Obtained (23%) from the title product of Preparation 54 following the experimental procedure described in Preparation 31.

$\delta(CDCl_3)$: 0.54 (m, 4H), 1.51 (m, 1H), 2.21 (s, 3H), 4.16 (d, 2H), 7.22 (m, 3H), 7.45 (m, 1H).

PREPARATION 56

4-(3-Fluorophenyl)-6-isopropyl-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (37%) from the title compound of Preparation 10 following the experimental procedure described in Preparation 46.

$\delta(CDCl_3)$: 1.38 (d, 6H), 2.58 (s, 3H), 5.41 (m, 1H), 7.32 (m, 3H), 7.52 (m, 1H).

PREPARATION 57

5-Acetyl-6-(3-fluorophenyl)-2-isopropyl-4-nitropyridazin-3(2H)-one

Obtained (40%) from the title product of Preparation 56 following the experimental procedure described in Preparation 31.

$\delta(CDCl_3)$: 1.44 (d, 6H), 2.20 (s, 3H), 5.45 (m, 1H), 7.16 (m, 3H), 7.50 (m, 1H).

PREPARATION 58

6-(Cyclopropylmethyl)-4-(4-fluorophenyl)-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (46%) from the title compound from Preparation 9 and cyclopropylmethyl bromide following the experimental procedure described in Preparation 17. The product was purified by column chromatography.

$\delta(CDCl_3)$: 0.54 (m, 4H), 1.38 (m, 1H), 2.58 (s, 3H), 4.08 (d, 2H), 7.28 (d, 2H), 7.57 (dd, 2H).

PREPARATION 59

5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-nitropyridazin-3(2H)-one

Obtained (37%) from the title product of Preparation 58 following the experimental procedure described in Preparation 31.

$\delta(CDCl_3)$: 0.46 (m, 2H), 0.62 (m, 2H), 1.45 (m, 1H), 2.21 (s, 3H), 4.18 (d, 2H), 7.21 (m, 2H), 7.45 (m, 2H).

PREPARATION 60

5-Methyl-4-(naphthalene-1-carbonyl)isoxazole-3-carboxylic acid ethyl ester

Obtained as a solid (90%) from 1-naphthalen-1-yl-butane-1,3-dione (Banchetti et al; *Gazz. Chim. Ital.*; **1940**, *70*, 134-40) following the procedure of Preparation 2.

$\delta(CDCl_3)$: 0.8 (t, 3H), 2.61 (s, 3H), 3.81 (q, 2H), 7.40-8.61 (m, 7H).

PREPARATION 61

3-Methyl-4-naphthalen-1-yl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (50%) from the title compound of Preparation 60 following the procedure of Preparation 7.

$\delta(CDCl_3)$: 1.99 (s, 3H), 7.43-8.10 (m, 7H), 9.82 (s, 1H).

PREPARATION 62

6-Ethyl-3-methyl-4-naphthalen-1-yl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (90%) from the title compound of Preparation 61 following the procedure of Preparation 17.

$\delta(CDCl_3)$: 1.46 (t, 3H), 1.97 (s, 3H), 4.37 (q, 2H), 7.43-7.76 (m, 5H), 7.96-8.07 (m, 2H).

PREPARATION 63

5-Acetyl-4-amino-2-ethyl-6-(naphthalen-1-yl)pyridazin-3(2H)-one

Obtained as a solid (85%) from the title compound of Preparation 62 following the procedure of Preparation 23.

$\delta(CDCl_3)$: 1.44 (t, 3H), 1.59 (s, 3H), 4.28 (q, 2H), 7.44-8.00 (m, 7H).

PREPARATION 64

6-Ethyl-4-phenyl-1,6-dihydroisoxazolo[3,4-d]pyridazine-3,7-dione

To a stirred solution of PPA (354g) in 354 mL of ethanol at 0°C, ethylhydrazine oxalate (14.58 g, 97.09 mmol) and the title compound of Preparation 37 (5.9 g, 97.09 mmol) were added portionwise. The resulting mixture was stirred at 40°C overnight. Then it was let to cool down to room temperature and water was carefully added until a precipitate appeared. It was stirred for 1 h at 0°C and then the final product was collected by filtration and washed with ethanol (2.04 g, 35% yield).

$\delta(CDCl_3)$: 1.44 (t, 3H), 4.30 (q, 2H), 7.42 (m, 3H), 7.90 (m, 2H).

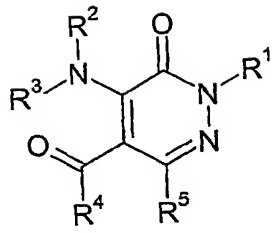
PREPARATION 65

6-Ethyl-1-(3-fluorophenyl)-4-phenyl-1,6-dihydroisoxazolo[3,4-d]pyridazine-3,7-dione

A mixture of the title compound of Preparation 64 (1.03 g, 4 mmol), 3-fluorophenylboronic acid (1.12 g, 8.0 mmol), anhydrous cupric acetate (1.09 g, 6.0 mmol), triethylamine (1.11 ml, 8.0 mmol) and activated molecular sieves (2.9 g, 4 Å) in dry dichloromethane (50 ml) was stirred under air exposure at room temperature overnight. The reaction mixture was filtered through a SiO_2 pad and eluted with dichloromethane. The solvent was removed under reduced pressure to yield the title product (500 mg, 36% yield).

$\delta(CDCl_3)$: 1.45 (t, 3H), 4.32 (q, 2H), 7.12 (m, 1H), 7.42 (m, 3H), 7.52 (m, 3H), 7.85 (m, 2H).

EXAMPLES



(I)

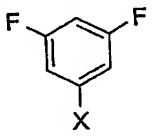
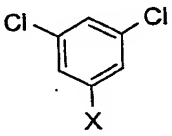
The following abreviations and their corresponding meanings have been used in the tables below:

Me	Methyl
MeO	Methoxy
Et	Ethyl
EtO	Ethoxy
iPr	isopropyl
iPrO	isopropoxy
NPr	n-propyl
Bn	Benzyl
BnO	Benzyloxy
NBu	n-butyl
Pyr	Pyridyl
Ph	Phenyl
(3-Ac)Ph	3-acetylphenyl
(4-Ac)Ph	4-acetylphenyl
(2-Br)Ph	2-bromophenyl
(3-Br)Ph	3-bromophenyl
(4-Br)Ph	4-bromophenyl
(2-CF_3)Ph	2-trifluoromethylphenyl
(3-CF_3)Ph	3-trifluoromethylphenyl
(2-CF_3O)Ph	2-trifluoromethoxyphenyl
(4-CF_3O)Ph	4-trifluoromethoxyphenyl
(4-CH_3CONH)Ph	4-acetamidophenyl
(2-Cl)Ph	2-chlorophenyl
(3-Cl)Ph	3-chlorophenyl
(4-Cl)Ph	4-chlorophenyl

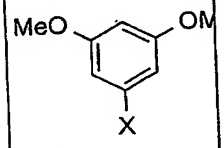
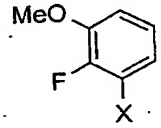
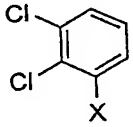
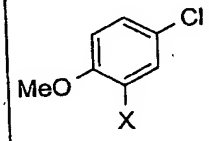
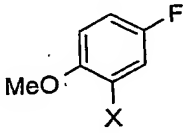
(2-CN)Ph	2-cyanophenyl
(3-CN)Ph	3-cyanophenyl
(4-CN)Ph	4-cyanophenyl
(2-$CONH_2$)Ph	2-carbamoylphenyl
(3-$CONH_2$)Ph	3-carbamoylphenyl
(4-$CONH_2$)Ph	4-carbamoylphenyl
(2-CO_2H)Ph	2-carboxyphenyl
(3-CO_2H)Ph	3-carboxyphenyl
(4-CO_2H)Ph	4-carboxyphenyl
(4-CO_2Me)Ph	4-methoxycarbonylphenyl
(4-CO_2Et)Ph	4-ethoxycarbonylphenyl
(3-EtO)Ph	3-ethoxyphenyl
(2-F)Ph	2-fluorophenyl
(3-F)Ph	3-fluorophenyl
(4-F)Ph	4-fluorophenyl
(4-H_2NCH_2)Ph	4-aminomethylphenyl
(2-$HOCH_2$)Ph	2-hydroxymethylphenyl
(3-$HOCH_2$)Ph	3-hydroxymethylphenyl
(4-$HOCH_2$)Ph	4-hydroxymethylphenyl
(2-Me)Ph	2-methylphenyl
(3-Me)Ph	3-methylphenyl
(4-Me)Ph	4-methylphenyl
(4-Me_2N)Ph	4-dimethylaminophenyl
(2-MeO)Ph	2-methoxyphenyl
(3-MeO)Ph	3-methoxyphenyl
(4-MeO)Ph	4-methoxyphenyl
(3-MeS)Ph	3-methylthiophenyl
(4-MeS)Ph	4-methylthiophenyl
(4-MeSO)Ph	4methylsulfinylphenyl
(2-NO_2)Ph	2-nitrophenyl
(3-NO_2)Ph	3-nitrophenyl
(4-NO_2)Ph	4-nitrophenyl
(3-OH)Ph	3-hydroxyphenyl
(4-Ph)Ph	4-phenylphenyl
(4-Pyr)CH_2	4-pyridylmethyl

(2-SO_2NH_2)Ph	2-sulfamoylphenyl
(4-SO_2NH_2)Ph	4-sulfamoylphenyl
(4-SO_2NH(nBu))Ph	4-(N-n-butyl)sulfamoylphenyl
(3-SH)Ph	3-mercaptophenyl
(4-tBu)Ph	4-tert-butylphenyl

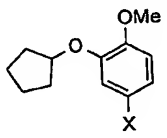
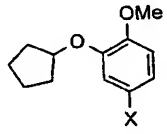
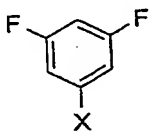
Table 2

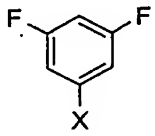
No.	R1	R2	R3	R4	R5
1	Et	H	(3-F)Ph	Me	Ph
2	Et	H		Me	Ph
3	Et	H		Me	Ph
4	Et	H	(3-NO_2)Ph	Me	Ph
5	Et	H	(4-Me)Ph	Me	Ph
6	Et	H	(2-Me)Ph	Me	Ph
7	Et	H	(2-MeO)Ph	Me	Ph

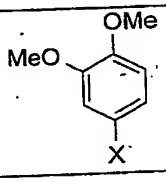
No.	R1	R2	R3	R4	R5
8	Et	H	1-Naphtyl	Me	Ph
9	Et	H	(4-MeS)Ph	Me	Ph
10	Et	H	(4-Ac)Ph	Me	Ph
11	Et	H	(4-Me_2N)Ph	Me	Ph
12	Et	H	2-Naphtyl	Me	Ph
13	Et	H	(2-Cl)Ph	Me	Ph
14	Et	H	(2-CF_3O)Ph	Me	Ph
15	Et	H	(2-CF_3)Ph	Me	Ph

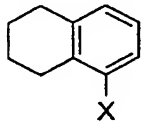
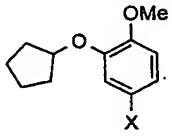
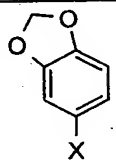
No.	R1	R2	R3	R4	R5
16	Et	H		Me	Ph
17	Et	H		Me	Ph
18	Et	H		Me	Ph
19	Et	H		Me	Ph
20	Et	H		Me	Ph
21	Et	H	(4-CO_2Me)Ph	Me	(4-MeS)Ph
22	Et	H	(3-F)Ph	Me	(4-MeS)Ph
23	Et	H	(4-CO_2H)Ph	Me	(4-MeS)Ph

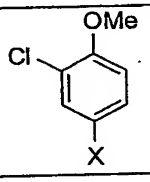
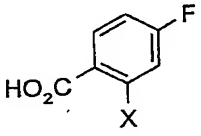
No.	R1	R2	R3	R4	R5
24	Et	H	1-Naphtyl	Me	(4-MeS)Ph
25	Et	H	(3-F)Ph	nPr	(4-MeS)Ph
26	Et	H	(3-F)Ph	$(CH_3CH_2)_2CH$	(4-MeS)Ph
27	Et	H	1-Naphtyl	$(CH_3CH_2)_2CH$	(4-MeS)Ph
28	Et	H	(4-CO_2Me)Ph	Me	(4-MeSO)Ph
29	Et	H	(3-F)Ph	Me	(4-MeSO)Ph
30	Et	H	(3-Cl)Ph	Me	(4-MeSO)Ph
31	Et	H	(2-Me)Ph	Me	(4-MeSO)Ph

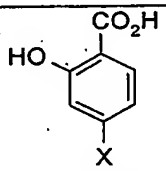
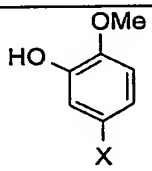
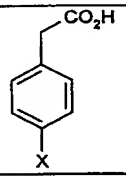
No.	R1	R2	R3	R4	R5
32	Et	H	1-Naphtyl	Me	(4-MeSO)Ph
33	Et	H	(3-NO_2)Ph	Me	(4-MeSO)Ph
34	Et	H	(2-MeO)Ph	Me	(4-MeSO)Ph
35	Et	H	(3-MeO)Ph	Me	(4-MeSO)Ph
36	Et	H	(3-F)Ph	Me	
37	Et	H	1-Naphtyl	Me	
38	Me	H	1-Naphtyl	Me	Ph
39	Me	H		Me	Ph

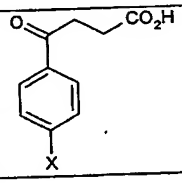
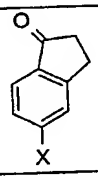
No.	R1	R2	R3	R4	R5
40	Me	H	(3-Cl)Ph	Me	Ph
41	Bn	H		Me	Ph
42	Bn	H	(3-F)Ph	Me	Ph
43	Bn	H	(3-Cl)Ph	Me	Ph
44	$C_3H_5CH_2$	H	1-Naphtyl	Me	Ph
45	$C_3H_5CH_2$	H	(3-F)Ph	Me	Ph
46	$C_3H_5CH_2$	H	(3-Cl)Ph	Me	Ph
47	(4-Pyr)CH_2	H	1-Naphtyl	Me	Ph

No.	R1	R2	R3	R4	R5
48	(4-Pyr)CH_2	H	(3-F)Ph	Me	Ph
49	Et	H	(3-Me)Ph	Me	Ph
50	Et	H	(4-CO_2H)Ph	Me	Ph
51	Et	H	(2-CO_2H)Ph	Me	Ph
52	Et	H	(3-Cl)Ph	Me	Ph
53	Et	H	(3-Br)Ph	Me	Ph
54	Et	H		Me	Ph
55	Et	H	(4-$HOCH_2$)Ph	Me	Ph

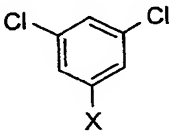
No.	R1	R2	R3	R4	R5
56	Et	H	(4-Ph)Ph	Me	Ph
57	Et	H		Me	Ph
58	Et	H		Me	Ph
59	Et	Me	Ph	Me	Ph
60	Et	H		Me	Ph
61	Et	H	(4-MeO)Ph	Me	Ph
62	Et	H	(4-Cl)Ph	Me	Ph
63	Et	H	(4-Br)Ph	Me	Ph

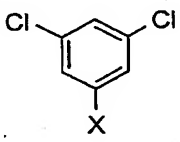
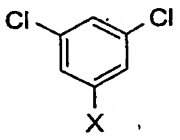
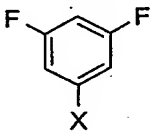
No.	R1	R2	R3	R4	R5
64	Et	H	(3-CF3)Ph	Me	Ph
65	Et	H		Me	Ph
66	Et	H	(3-OH)Ph	Me	Ph
67	Et	H	(3-CO_2H)Ph	Me	Ph
68	Et	H	(2-F)Ph	Me	Ph
69	Et	H	(4-CO2Et)Ph	Me	Ph
70	Et	H	(4-F)Ph	Me	Ph
71	Et	H		Me	Ph

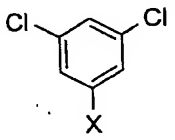
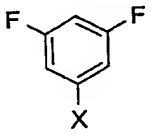
No.	R1	R2	R3	R4	R5
72	Et	H	(3-CN)Ph	Me	Ph
73	Et	H		Me	Ph
74	Et	H		Me	Ph
75	Et	H	(4-$CONH_2$)Ph	Me	Ph
76	Et	H	(3-MeS)Ph	Me	Ph
77	Et	H	(3-MeO)Ph	Me	Ph
78	Et	H	(3-Ac)Ph	Me	Ph
79	Et	H		Me	Ph

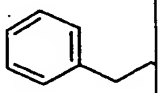
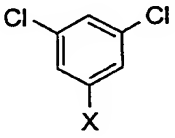
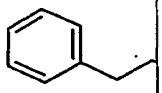
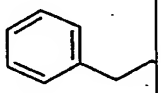
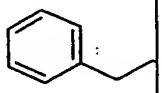
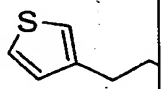
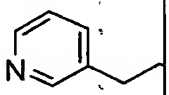
No.	R1	R2	R3	R4	R5
80	Et	H	(4-tBu)Ph	Me	Ph
81	Et	H	(4-SO_2NH_2)Ph	Me	Ph
82	Et	H		Me	Ph
83	Et	H	[4-SO_2NH(nBu)]Ph	Me	Ph
84	Et	H		Me	Ph
85	Et	H	(4-CH_3CONH)Ph	Me	Ph
86	Et	H	(4-CO_2H)Ph	Me	(3-Cl)Ph
87	Et	H	(3-Cl)Ph	Me	(3-Cl)Ph

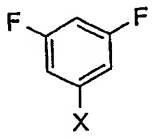
No.	R1	R2	R3	R4	R5
88	Et	H	(3-F)Ph	Me	(3-Cl)Ph
89	Et	H	(3-Cl)Ph	Me	(4-F)Ph
90	Et	H	(3-Br)Ph	Me	(3-F)Ph
91	Et	H	(3-F)Ph	Me	(3-F)Ph
92	Et	H	(3-Cl)Ph	Me	(3-F)Ph
93	Et	H	(3-Cl)Ph	Me	(3-NO_2)Ph
94	Et	H	(3-F)Ph	Me	(3-NO_2)Ph
95	Et	H	(4-CO_2H)Ph	Me	(3-NO_2)Ph

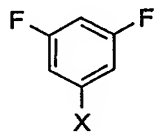
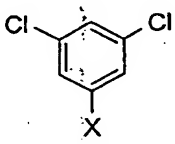
No.	R1	R2	R3	R4	R5
96	Et	H	(3-Br)Ph	Me	(3-NO_2)Ph
97	Et	H	1-Naphtyl	Me	(3-NO_2)Ph
98	Et	H	(3-Cl)Ph	nPr	Ph
99	NPr	H	(3-Cl)Ph	Me	Ph
100	NBu	H	(3-Cl)Ph	Me	Ph
101	NBu	H	(3-Br)Ph	Me	Ph
102	Et	(3-F)Ph		Me	Ph
103	Et	(3-F)Ph	(3-F)Ph	Me	Ph

No.	R1	R2	R3	R4	R5
104	Et	(3-Cl)Ph	(3-Cl)Ph	Me	Ph
105	Et	(4-MeS)Ph	(4-MeS)Ph	Me	Ph
106	Et	(4-Ac)Ph	(4-Ac)Ph	Me	Ph
107	Et			Me	Ph
108	Et	(4-CO_2Me)Ph	(4-CO_2Me)Ph	Me	(4-MeSO)Ph
109	$C_3H_5CH_2$	H		Me	Ph
110	Me	H	(3-F)Ph	Me	Ph
111	Me	H	(4-CO_2H)Ph	Me	Ph

No.	R1	R2	R3	R4	R5
112	Ph	H		Me	Ph
113	Ph	H	(3-F)Ph	Me	Ph
114	Ph	H	1-Naphtyl	Me	Ph
115	Ph	H		Me	Ph
116	Ph	H	(3-Cl)Ph	Me	Ph
117	Et	H	(3-Cl)Ph	Ph	Ph
118	Et	H	(3-Cl)Ph	H	Ph
119	Et	H	(3-Cl)Ph	MeO	Ph

No.	R1	R2	R3	R4	R5
120	Et	H	(3-Cl)Ph		Ph
121	Et	H			Ph
122	Et	H	(3-CN)Ph		Ph
123	Et	H	(4-CO2H)Ph		Ph
124	Et	H	(3-Cl)Ph		Ph
125	Et	H	(3-Cl)Ph		Ph
126	Bn	H	1-Naphthyl	Me	Ph
127	Bn	H	(4-CO2H)Ph	Me	Ph

No.	R1	R2	R3	R4	R5
128	(4-Pyr)CH2	H		Me	Ph
129	(4-Pyr)CH2	H	(3-Cl)Ph	Me	Ph
130	Ph	H	(4-CO2H)Ph	Me	Ph
131	C3H5CH2	H	(2-F)Ph	Me	Ph
132	C3H5CH2	H	(2-Cl)Ph	Me	Ph
133	C3H5CH2	H	(4-HOCH2)Ph	Me	Ph
134	C3H5CH2	H	(3-CN)Ph	Me	Ph
135	C3H5CH2	H	(4-CO2H)Ph	Me	Ph

No.	R1	R2	R3	R4	R5
136	iPr	H	1-Naphthyl	Me	Ph
137	iPr	H		Me	Ph
138	iPr	H	(3-F)Ph	Me	Ph
139	iPr	H	(3-Cl)Ph	Me	Ph
140	iPr	H		Me	Ph
141	iPr	H	(4-CO2H)Ph	Me	Ph
142	iPr	H	(2-F)Ph	Me	Ph
143	iPr	H	(2-Cl)Ph	Me	Ph

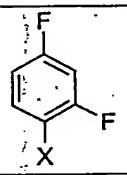
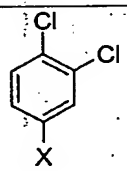
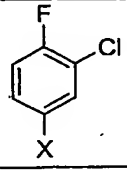
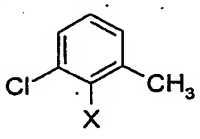
No.	R1	R2	R3	R4	R5
144	iPr	H	(3-CN)Ph	Me	Ph
145	iPr	H	(4-HOCH2)Ph	Me	Ph
146	HOCH2CH2	H	(2-F)Ph	Me	Ph
147	HOCH2CH2	H	(2-Cl)Ph	Me	Ph
148	HOCH2CH2	H	(3-CN)Ph	Me	Ph
149	HOCH2CH2	H	(4-HOCH2)Ph	Me	Ph
150	HOCH2CH2	H	(3-Cl)Ph	Me	Ph
151	HOCH2CH2	H	(2-F)Ph	Me	(3-F)Ph

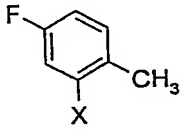
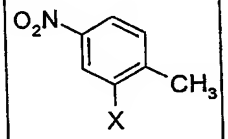
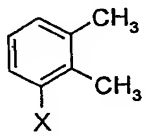
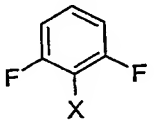
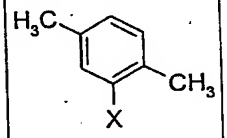
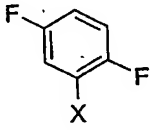
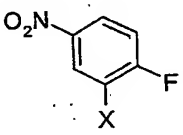
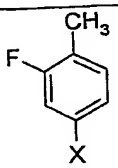
No.	R1	R2	R3	R4	R5
152	HOCH2CH2	H	(2-Cl)Ph	Me	(3-F)Ph
153	HOCH2CH2	H	(3-CN)Ph	Me	(3-F)Ph
154	HOCH2CH2	H	(4-HOCH2)Ph	Me	(3-F)Ph
155	HOCH2CH2	H	(3-Cl)Ph	Me	(3-F)Ph
156	C3H5CH2	H	(3-CONH2)Ph	Me	(3-Cl)Ph
157	C3H5CH2	H	(4-HOCH2)Ph	Me	(3-Cl)Ph
158	C3H5CH2	H	(3-CN)Ph	Me	(3-Cl)Ph
159	C3H5CH2	H	(2-F)Ph	Me	(3-Cl)Ph

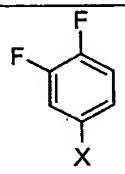
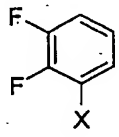
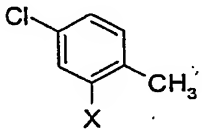
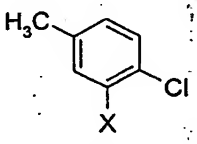
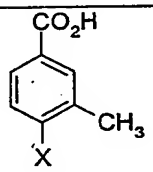
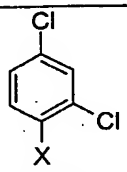
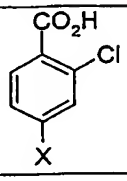
No.	R1	R2	R3	R4	R5
160	C3H5CH2	H	(3-Cl)Ph	Me	(3-Cl)Ph
161	C3H5CH2	H	(3-CONH2)Ph	Me	(3-F)Ph
162	C3H5CH2	H	(4-HOCH2)Ph	Me	(3-F)Ph
163	iPr	H	(3-CONH2)Ph	Me	(3-F)Ph
164	iPr	H	(4-HOCH2)Ph	Me	(3-F)Ph
165	iPr	H	(3-CN)Ph	Me	(3-F)Ph
166	iPr	H	(2-F)Ph	Me	(3-F)Ph
167	iPr	H	(3-Cl)Ph	Me	(3-F)Ph

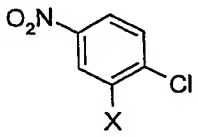
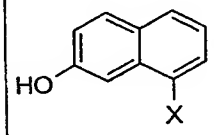
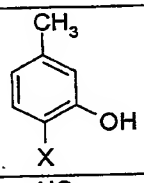
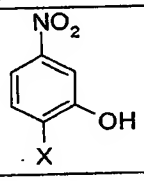
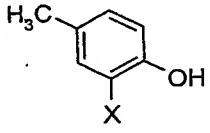
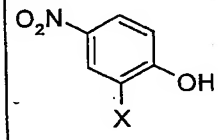
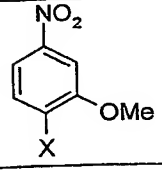
No.	R1	R2	R3	R4	R5
168	iPr	H	(2-Cl)Ph	Me	(3-F)Ph
169	C3H5CH2	H	(3-CN)Ph	Me	(4-F)Ph
170	C3H5CH2	H	(3-CONH2)Ph	Me	(4-F)Ph
171	Et	H	(3-CONH2)Ph	Me	(3-Cl)Ph
172	Et	H	(4-HOCH2)Ph	Me	(3-Cl)Ph
173	Et	H	(3-CN)Ph	Me	(3-Cl)Ph
174	Et	H	(2-F)Ph	Me	(3-Cl)Ph
175	Et	H	(2-Cl)Ph	Me	(3-Cl)Ph

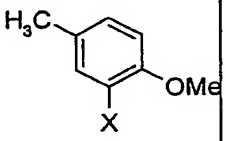
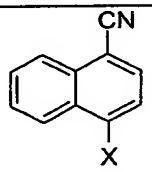
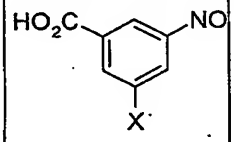
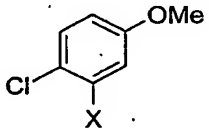
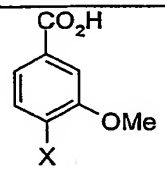
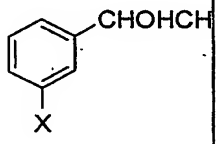
No.	R1	R2	R3	R4	R5
176	Et	H	(4-HOCH2)Ph	Me	(3-F)Ph
177	Et	H	(3-CONH2)Ph	Me	(3-F)Ph
178	Et	H	(3-CN)Ph	Me	(3-F)Ph
179	Et	H	(2-F)Ph	Me	(3-F)Ph
180	Et	H	(2-Cl)Ph	Me	(3-F)Ph
181	Et	H	(4-HOCH2)Ph	Me	(4-F)Ph
182	Et	H	(4-CN)Ph	Me	(4-F)Ph
183	Et	H	(3-CONH2)Ph	Me	(4-F)Ph

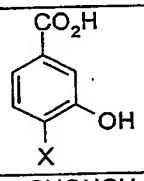
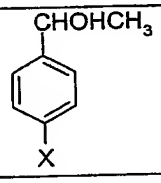
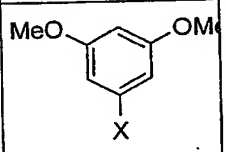
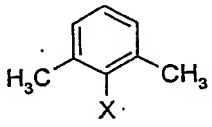
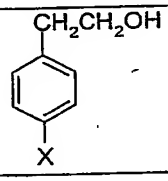
No.	R1	R2	R3	R4	R5
184	Et	H	(3-CN)Ph	Me	(4-F)Ph
185	Et	H	(2-F)Ph	Me	(4-F)Ph
186	Et	H	(2-Cl)Ph	Me	(4-F)Ph
187	Et	H	(3-Cl)Ph	Me	1-Naphthyl
188	Et	H		Me	Ph
189	Et	H		Me	Ph
190	Et	H		Me	Ph
191	Et	H		Me	Ph

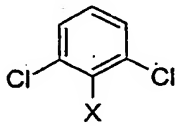
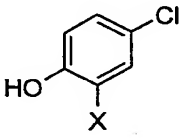
No.	R1	R2	R3	R4	R5
192	Et	H		Me	Ph
193	Et	H		Me	Ph
194	Et	H		Me	Ph
195	Et	H		Me	Ph
196	Et	H		Me	Ph
197	Et	H		Me	Ph
198	Et	H		Me	Ph
199	Et	H		Me	Ph

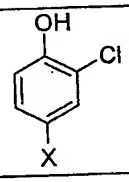
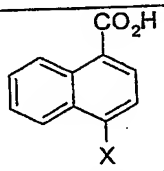
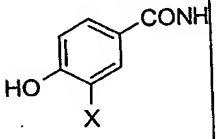
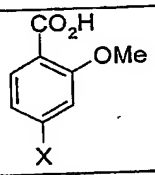
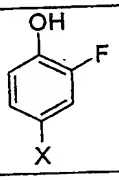
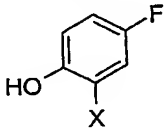
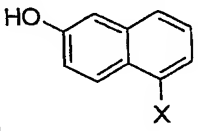
No.	R1	R2	R3	R4	R5
200	Et	H		Me	Ph
201	Et	H	(2-Br)Ph	Me	Ph
202	Et	H		Me	Ph
203	Et	H		Me	Ph
204	Et	H		Me	Ph
205	Et	H		Me	Ph
206	Et	H		Me	Ph
207	Et	H		Me	Ph

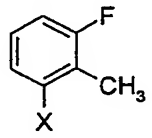
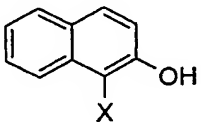
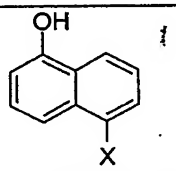
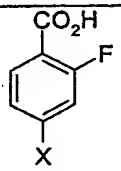
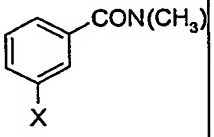
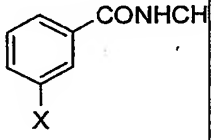
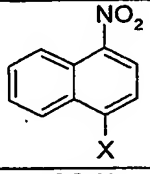
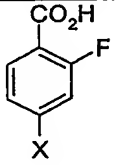
No.	R1	R2	R3	R4	R5
208	Et	H		Me	Ph
209	Et	H		Me	Ph
210	Et	H		Me	Ph
211	Et	H		Me	Ph
212	Et	H		Me	Ph
213	Et	H		Me	Ph
214	Et	H		Me	Ph
215	Et	H	(4-CF3O)Ph	Me	Ph

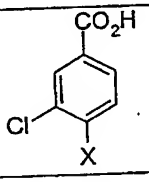
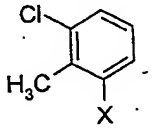
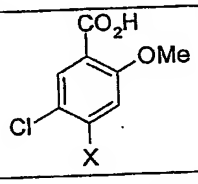
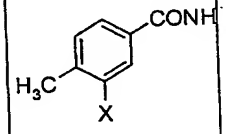
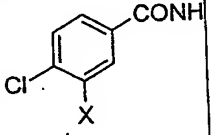
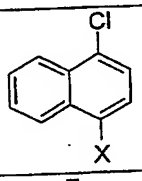
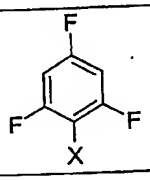
No.	R1	R2	R3	R4	R5
216	Et	H	(3-EtO)Ph	Me	Ph
217	Et	H		Me	Ph
218	Et	H		Me	Ph
219	Et	H		Me	Ph
220	Et	H	(3-SH)Ph	Me	Ph
221	Et	H		Me	Ph
222	Et	H		Me	Ph
223	Et	H		Me	Ph

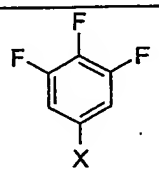
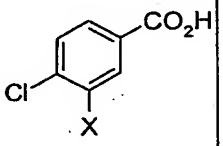
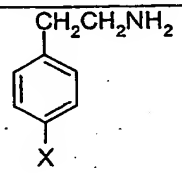
No.	R1	R2	R3	R4	R5
224	Et	H	(3-HOCH2)Ph	Me	Ph
225	Et	H		Me	Ph
226	Et	H		Me	Ph
227	Et	H		Me	Ph
228	Et	H		Me	Ph
229	Et	H		Me	Ph
230	Et	H	(4-NO2)Ph	Me	Ph
231	Et	H	(4-CN)Ph	Me	Ph

No.	R1	R2	R3	R4	R5
232	Et	H	(3-CONH2)Ph	Me	Ph
233	Et	H	(2-HOCH2)Ph	Me	Ph
234	Et	H	(2-CONH2)Ph	Me	Ph
235	Et	H	(2-SO2NH2)Ph	Me	Ph
236	Et	H	(2-CN)Ph	Me	Ph
237	Et	H		Me	Ph
238	Et	H	(2-NO2)Ph	Me	Ph
239	Et	H		Me	Ph

No.	R1	R2	R3	R4	R5
240	Et	H		Me	Ph
241	Et	H	(4-SO2NH2)Ph	Me	Ph
242	Et	H		Me	Ph
243	Et	H		Me	Ph
244	Et	H		Me	Ph
245	Et	H		Me	Ph
246	Et	H		Me	Ph
247	Et	H		Me	Ph

No.	R1	R2	R3	R4	R5
248	Et	H		Me	Ph
249	Et	H		Me	Ph
250	Et	H		Me	Ph
251	Et	H		Me	Ph
252	Et	H		Me	Ph
253	Et	H		Me	Ph
254	Et	H		Me	Ph
255	Et	H		Me	Ph

No.	R1	R2	R3	R4	R5
256	Et	H		Me	Ph
257	Et	H		Me	Ph
258	Et	H	(4-CO2Me)Ph	Me	Ph
259	Et	H		Me	Ph
260	Et	H		Me	Ph
261	Et	H		Me	Ph
262	Et	H		Me	Ph
263	Et	H		Me	Ph

No.	R1	R2	R3	R4	R5
264	Et	H		Me	Ph
265	Et	H		Me	Ph
266	Et	H	(4-H2NCH2)Ph	Me	Ph
267	Et	H		Me	Ph
268	Et	H	(3-F)Ph	Me	(4-MeS)Ph
269	Et	H	(3-F)Ph	OH	Ph
270	Et	H	(3-Cl)Ph	OH	Ph
271	Et	H	(3-F)Ph	MeO	Ph

No.	R1	R2	R3	R4	R5
272	Et	H	(3-Cl)Ph	iPrO	Ph
273	Et	H	(3-Cl)Ph	EtO	Ph
274	Et	H	(3-Cl)Ph	BnO	Ph

The symbol X in the structures shows only the binding point. It does not represent any atom.

EXAMPLE 1

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

A mixture of the title compound of Preparation 22 (250 mg, 0.97 mmol), 3-fluorophenylboronic acid (272 mg, 1.94 mmol), anhydrous cupric acetate (265 mg, 1.46 mmol), triethylamine (0.27 ml, 1.94 mmol) and activated molecular sieves (720 mg, 4 Å) in dry dichloromethane (12 ml) was stirred under air exposure at room temperature for 24 h. The reaction was filtered and the solvent removed under reduced pressure. The resulting residue was purified by flash column cromathography (SiO_2, dichloromethane-ethyl acetate) to yield the title product (216 mg, 63% yield).

m.p. 176.5-178.2°C.

δ($CDCl_3$): 1.45 (t, 3H), 1.74 (s, 3H), 4.30 (q, 2H), 6.76 (m, 1H), 6.85 (m, 2H), 7.25 (m, 1H), 7.40 (m, 5H), 8.24 (s, 1H).

EXAMPLE 2

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

Obtained as a solid (54%) from the title compound of Preparation 22 and 3,5-difluorophenylboronic acid following the procedure of Example 1.

m.p. 243.4-244.6°C.

δ($CDCl_3$): 1.44 (t, 3H), 1.80 (s, 3H), 4.31 (q, 2H), 6.59 (m, 3H), 7.40 (m, 5H), 8.26 (s, 1H).

EXAMPLE 3

5-Acetyl-4-[(3,5-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one.

Obtained as a solid (55%) from the title compound of Preparation 22 and 3,5-dichlorophenylboronic acid following the procedure of Example 1.

m.p. 254.4-254.6°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.84 (s, 3H), 4.17 (q, 2H), 7.1 (s, 1H), 7.19 (m, 2H), 7.38 (m, 5H), 9.14 (s, 1H).

EXAMPLE 4

5-Acetyl-2-ethyl-4-[(3-nitrophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

Obtained as a solid (40%) from the title compound of Preparation 22 and 3-nitrophenylboronic acid following the procedure of Example 1.

m.p. 241.8-243.7°C.

δ($CDCl_3$): 1.45 (t, 3H), 1.78 (s, 3H), 4.31 (q, 2H), 7.45 (m, 7H), 7.84 (s,1H), 8.02 (d, 1H), 8.73 (s, 1H).

EXAMPLE 5

5-Acetyl-2-ethyl-4-[(4-methylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

Obtained as a solid (50%) from the title compound of Preparation 22 and 4-methylphenylboronic acid following the procedure of Example 1.

LRMS: m/Z 347 $(M+1)^+$.

δ($CDCl_3$): 1.46 (t, 3H), 1.58 (s, 3H), 2.34 (s, 3H), 4.31 (q, 2H), 6.95 (d, 2H), 7.13 (d, 2H), 7.34 (m, 5H), 8.03 (s, 1H).

EXAMPLE 6

5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-phenylpyridazin-3(2*H*) -one

Obtained as a solid (54%) from the title compound of Preparation 22 and 2-methylphenylboronic acid following the procedure of Example 1.

m.p. 189.8- 190.7°C.

δ($CDCl_3$): 1.46 (t, 3H), 1.51 (s, 3H), 2.33 (s, 3H), 4.31 (q, 2H), 6.97 (d, 1H), 7.11 (m, 2H), 7.23 (m, 1H), 7.34 (m, 5H), 7.81 (s, 1H).

EXAMPLE 7

5-Acetyl-2-ethyl-4-[(2-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

Obtained as a solid (30%) from the title compound of Preparation 22 and 2-methoxyphenylboronic acid following the procedure of Example 1.

m.p. 205.4- 206.8°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.52 (s, 3H), 3.73 (s, 3H), 4.16 (q, 2H), 6.85 (t, 1H), 6.97 (d, 1H), 7.02 (d, 1H), 7.14 (t, 1H), 7.26 (m, 2H), 7.36 (m, 3H), 8.47 (s, 1H).

EXAMPLE 8

5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2H)-one

Obtained as a solid (51%) from the title compound of Preparation 22 and 1-naphthylboronic acid following the procedure of Example 1.

m.p. 196.8 - 197.7°C.

δ($CDCl_3$): 1.23 (s, 3H), 1.52 (t, 3H), 4.36 (q, 2H), 6.85 (t, 1H), 7.34 (m, 6H), 7.58 (m, 2H), 7.75 (d, 1H), 7.86 (d, 1H), 8.12 (d, 1H), 8.27 (s, 1H).

EXAMPLES 9-20

5-Acetyl-2-ethyl-4-{[4-(methylthio)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(4-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-{[4-(dimethylamino)phenyl]amino}-2-ethyl-6-phenylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-(2-naphthylamino)-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-phenyl-4-([3-(trifluoromethoxy)phenyl]amino)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-phenyl-4-([2-(trifluoromethyl)phenyl]amino)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(2,5-dimethoxyphenyl)amino]-6-phenylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-[(2-fluoro-3-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(2,3-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(5-chloro-2-methoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(5-fluoro-2-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

The title compounds were synthesized from the title compound of Preparation 22 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 3.

Table 3

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
9	380	9.3
10	376	8.4
11	377	8.7
12	384	9.6
13	368	9.3
14	418	9.8
15	402	9.7
16	394	8.9
17	382	8.8
18	403	9.8
19	398	9.5
20	382	9.0

EXAMPLE 21

Methyl 4-({5-acetyl-2-ethyl-6-[4-(methylthio)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoate

Obtained as a solid (20%) from the title compound of preparation 23 and 4-(methoxycarbonyl)phenylboronic acid following the procedure of Example 1.

LRMS: m/Z 438 $(M+1)^+$.

Retention Time: 9.4 min.

$\delta(CDCl_3)$: 1.42 (t, 3H), 1.81 (s, 3H), 2.46 (s, 3H), 3.92 (s, 3H), 4.32 (q, 2H), 7.05 (d, 2H), 7.23 (m, 4H), 7.99 (d, 2H), 8.38 (s, 1H).

EXAMPLES 22-24

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one

4-({5-Acetyl-2-ethyl-6-[4-(methylthio)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoic acid

5-Acetyl-2-ethyl-6-[4-(methylthio)phenyl]-4-(1-naphthylamino)pyridazin-3(2*H*)-one

The title compounds were synthesized from the title compound of Preparation 23 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 4.

Table 4

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
22	398	9.5
23	424	8.7
24	430	10.0

EXAMPLE 25

5-Butyryl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 24 and 3-fluorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 426 $(M+1)^+$

Retention Time: 10.2 min

EXAMPLE 26

2-Ethyl-5-(2-ethylbutanoyl)-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 25 and 3-fluorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 454 $(M+1)^+$

Retention Time: 11.1 min

EXAMPLE 27

2-Ethyl-5-(2-ethylbutanoyl)-6-[4-(methylthio)phenyl]-4-(naphth-1-ylamino)pyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 25 and 1-naphtylboronic acid following the procedure of Example 1.

LRMS: m/Z 486 $(M+1)^+$

Retention Time: 10.8 min

EXAMPLE 28

Methyl 4-({5-acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoate

Obtained as a solid (20%) from the title compound of Preparation 26 and 4-(methoxycarbonyl)phenylboronic acid following the procedure of Example 1.

LRMS: m/Z 454 (M+1)+.

Retention Time: 7.2 min.

δ($CDCl_3$): 1.42 (t, 3H), 1.81 (s, 3H), 2.78 (s, 3H), 3.93 (s, 3H), 4.32 (q, 2H), 7.10 (d, 2H), 7.58 (d, 2H), 7.75 (d, 2H), 8.01 (d, 2H), 8.35 (s, 1H).

EXAMPLES 29-35

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-(1-naphthylamino)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(3-nitrophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(2-methoxyphenyl)amino]pyridazin-3(2H)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(3-methoxyphenyl)amino]pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 26 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 5.

Table 5

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
29	414	7.2
30	430	7.8
31	410	7.5
32	446	8.1
33	441	7.2
34	426	7.2
35	426	7.3

EXAMPLE 36

5-Acetyl-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 27 and 3-fluorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 466 $(M+1)^+$

Retention Time: 10.3 min

EXAMPLE 37

5-Acetyl-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-ethyl-4-(1-naphthylamino)pyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 27 and 1-naphtylboronic acid following the procedure of Example 1.

LRMS: m/Z 498 $(M+1)^+$

Retention Time: 10.8 min

EXAMPLES 38-40

5-Acetyl-2-methyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one

The title compounds were synthesized from 5-acetyl-4-amino-2-methyl-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., *Heterocycles*, **1991**, *32*, 1173-9) and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 6.

Table 6

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
38	370	9.1
39	356	8.8
40	354	9.0

EXAMPLES 41-43

5-Acetyl-2-benzyl-4-[(3,5-difluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-benzyl-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-benzyl-4-[(3-chlorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

The title compounds were synthesized from the title compound of Preparation 28 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 7.

Table 7

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
41	432	10.0
42	414	9.8
43	429	10.2

EXAMPLES 44-46

5-Acetyl-2-(cyclopropylmethyl)-4-(1-naphthylamino)-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-(cyclopropylmethyl)-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-phenylpyridazin-3(2*H*)-one

The title compounds were synthesized from the title compound of Preparation 29 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 8.

Table 8

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
44	410	10.1
45	378	9.5
46	394	9.9

EXAMPLE 47

5-Acetyl-4-(1-naphthylamino)-6-phenyl-2-pyridin-4-ylmethylpyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 30 and 1-naphtylboronic acid following the procedure of Example 1.

LRMS: m/Z 447 $(M+1)^+$

Retention Time: 8.6 min

EXAMPLE 48

5-Acetyl-4-[(3-fluorophenyl)amino]-6-phenyl-2-pyridin-4-ylmethylpyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 30 and 3-fluorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 415 $(M+1)^+$

Retention Time: 7.8 min

EXAMPLE 49

5-Acetyl-2-ethyl-4-[(3-methylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one.

To a stirred solution of 57 mg (0.20 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) (57 mg, 0.20 mmol) in ethanol (2 ml), *m*-toluidine (64 mg, 0.60 mmol) was added portionwise. The resulting

mixture was stirred at room temperature for 30 min and the final product was collected by filtration and washed with ethanol and diethylether to yield the title compound (24 mg, 35% yield).

LRMS: m/Z 348 (M+1)+.

Retention Time: 9.9 min.

δ($CDCl_3$): 1.42 (t, 3H), 1.57 (s, 3H), 2.50 (s, 3H), 4.30 (q, 2H), 6.87 (m, 2H), 7.03 (d, 1H), 7.17 (d,1H), 7.48 (m, 5H), 8.03 (s, 1H).

EXAMPLE 50

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-aminobenzoic acid following the procedure of Example 49. The product was recrystallized from ethanol/dichloromethane (76% yield).

m.p. 273.0- 273.4°C.

δ (DMSO-d6): 1.32 (t, 3H), 1.83 (s, 3H), 4.17 (q, 2H), 7.04 (d, 2H), 7.31 (m, 2H), 7.40 (m, 3H), 7.76 (d, 2H), 9.20 (s, 1H), 12.72 (bs, 1H).

EXAMPLE 51

2-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

Obtained (25%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2-aminobenzoic acid following the procedure of Example 49.

LRMS: m/Z 348 $(M+1)^+$.

δ(CDCl3): 1.42 (t, 3H), 1.83 (s, 3H), 4.18 (q, 2H), 6.82 (d, 1H), 7.07 (t, 1H), 7.42 (m, 6H), 8.02 (d, 1H), 10.02 (s, 1H), 12.72 (bs, 1H).

EXAMPLE 52

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

Obtained (64 %) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-chloroaniline following the procedure of Example 49.

m.p. 189.0-190.6°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.75 (s, 3H), 4.18 (q, 2H), 7.02 (m, 1H), 7.17 (m, 2H), 7.30 (m, 3H), 7.40 (m, 3H), 9.05 (s, 1H).

EXAMPLE 53

5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

Obtained (65 %) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-bromoaniline following the procedure of Example 49.

m.p. 191.3-192.1°C

δ(DMSO-d6): 1.33 (t, 3H), 1.75 (s, 3H), 4.17 (q, 2H), 7.03 (m, 1H), 7.22 (m, 3H), 7.30 (m, 2H), 7.42 (m, 3H), 9.06 (s, 1H).

EXAMPLE 54

5-Acetyl-4-[(3,4-dimethoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

Obtained (76 %) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3,4-dimethoxyaniline following the procedure of Example 49.

LRMS: m/Z 388 $(M+1)^+$

δ($CDCl_3$): 1.42 (t, 3H), 1.65 (s, 3H), 3.78 (m, 6H), 4.25 (q, 2H), 6.62 (m, 2H), 6.78 (m, 1H), 7.38 (m, 5H), 7.98 (s, 1H).

EXAMPLE 55

5-Acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one

Obtained (20%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and (4-aminophenyl)methanol following the procedure of Example 49.

LRMS: m/Z 388 $(M+1)^+$

δ($CDCl_3$): 1.62 (t, 3H), 1.84 (s, 3H), 2.10 (bs, 1H), 4.25 (q, 2H), 4.63 (s, 2H), 7.05 (d, 2H), 7.38 (m, 7H), 8.22 (s, 1H).

EXAMPLE 56

5-Acetyl-4-(1,1'-biphenyl-4-ylamino)-2-ethyl-6-phenylpyridazin-3(2*H*)-one

Obtained (22%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 1,1'-biphenyl-4-amine following the procedure of Example 49.

LRMS: m/Z 410 $(M+1)^+$

δ(CDCl3): 1.42 (t, 3H), 1.77 (s, 3H), 4.28 (q, 2H), 7.15 (d, 2H), 7.38 (m, 9H), 7.56 (m, 3H), 8.22 (s, 1H).

EXAMPLE 57

5-Acetyl-2-ethyl-6-phenyl-4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)pyridazin-3(2*H*)-one

Obtained (23%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 5,6,7,8-tetrahydronaphthalen-1-amine following the procedure of Example 49.

LRMS: m/Z 388 (M+1)+

$\delta(CDCl_3)$: 1.42 (t, 3H), 1.44 (s, 3H), 1.78 (m, 4H), 2.67 (m, 4H), 4.28 (q, 2H), 6.75 (m, 1H), 6.98 (m, 2H), 7.36 (m, 5H), 7.78 (s, 1H).

EXAMPLE 58

5-acetyl-4-{[3-(cyclopentyloxy)-4-methoxyphenyl]amino}-2-ethyl-6-phenylpyridazin-3(2*H*)-one

Obtained (23%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-(cyclopentyloxy)-4-methoxyaniline (World Patent Application WO9325517) following the procedure of Example 49.

LRMS: m/Z 448 $(M+1)^+$

$\delta(CDCl_3)$: 1.45 (m, 10H), 1.90 (m, 4H), 3.82 (s, 3H), 4.32 (q, 2H), 4.70 (m, 1H), 6.66 (m, 3H), 7.38 (m, 5H), 7.82 (s, 1H).

EXAMPLE 59

5-Acetyl-2-ethyl-4-[*N*-methyl-*N*-phenylamino]-6-phenylpyridazin-3(2H)-one

Obtained (28%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and *N*-methylaniline following the procedure of Example 49.

LRMS: m/Z 348 $(M+1)^+$

$\delta(CDCl_3)$: 1.42 (t, 3H), 1.83 (s, 3H), 3.28 (s, 3H), 4.32 (q, 2H), 6.78 (m, 2H), 6.90 (m, 1H), 7.25 (m, 1H), 7.42 (m, 6H).

EXAMPLES 60-85

5-Acetyl-4-(1,3-benzodioxol-5-ylamino)-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(4-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(4-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(4-bromophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-phenyl-4-{[3-(trifluoromethyl)phenyl]amino}pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chloro-4-methoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-hydroxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

5-Acetyl-2-ethyl-4-[(2-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

4-(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydro-pyridazin-4-ylamino)-benzoic acid ethyl ester

5-Acetyl-2-ethyl-4-[(4-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

2-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-4-fluorobenzoic acid

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-2-hydroxybenzoic acid

5-Acetyl-2-ethyl-4-[(3-hydroxy-4-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzamide

5-Acetyl-2-ethyl-4-{[3-(methylthio)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}acetic acid

5-Acetyl-4-[4-(*tert*-butylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzenesulphonamide

4-{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}-4-oxobutanoic acid

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-*N*-butylbenzenesulphonamide

5-acetyl-2-ethyl-4-[(1-oxo-2,3-dihydro-1H-inden-5-yl)amino]-6-phenylpyridazin-3(2H)-one

***N*-{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}acetamide**

The title compounds were synthesized from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and the corresponding

aniline following the procedure of Example 49. The ESI/MS data and HPLC retention times are summarized in Table 9.

Table 9

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
60	378	8.6
61	364	8.7
62	368	9.3
63	413	9.5
64	402	9.6
65	398	9.2
66	350	8.0
67	378	8.0
68	352	8.9
69	406	9.3
70	352	8.8
71	396	9.1
72	359	8.5
73	394	8.3
74	380	7.9
75	377	7.3
76	380	9.4
77	364	8.9
78	376	8.5
79	392	8.0
80	390	10.4
81	413	7.5
82	434	8.0
83	469	9.2
84	388	8.3
85	391	7.6

EXAMPLE 86

4-[5-Acetyl-6-(3-chlorophenyl)-2-ethyl-3-oxo-2,3-dihydropyridazin-4-ylamino]benzoic acid

Obtained (35%) from 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-aminobenzoic acid following the procedure of Example 49.

m.p. 207.0-207.9

$\delta(CDCl_3)$: 1.46 (t, 3H), 1.85 (s, 3H), 4.31 (q, 2H), 7.10 (d, 2H), 7.23 (m, 2H), 7.40 (m, 2H), 8.04 (d, 2H), 8.48 (s, 1H).

EXAMPLE 87

5-Acetyl-6-(3-chlorophenyl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2*H*)-one

Obtained from 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-chloroaniline following the procedure of Example 49.

LRMS: m/Z 403 $(M+1)^+$

Retention Time: 10.0 min

EXAMPLE 88

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

Obtained from 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-fluoroaniline following the procedure of Example 49.

LRMS: m/Z 386 $(M+1)^+$

Retention Time: 9.6 min

EXAMPLE 89

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(4-fluorophenyl)pyridazin-3(2*H*)-one

Obtained (71 %) from the title compound of Preparation 31 and 3-chloroaniline following the procedure of Example 49.

m.p. 190.9-191.4

$\delta(CDCl_3)$: 1.45 (t, 3H), 1.75 (s, 3H), 4.29 (q, 2H), 6.97 (d, 1H), 7.01 (m, 4H), 7.26 (m, 1H), 7.36 (m, 2H), 8.17 (s, 1H).

EXAMPLE 90

5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2*H*)-one

Obtained (85 %) from the title compound of Preparation 32 and 3-bromoaniline following the procedure of Example 49.

m.p. 169.0-170.7

$\delta(CDCl_3)$: 1.45 (t, 3H), 1.77 (s, 3H), 4.29 (q, 2H), 7.01-7.38 (m, 8H), 8.22 (s, 1H).

EXAMPLE 91

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-(3-fluorophenyl)pyridazin-3(2H)-one

Obtained (84 %) from the title compound of Preparation 32 and 3-fluoroaniline following the procedure of Example 49.

m.p. 173.5-174.6

$\delta(CDCl_3)$: 1.45 (t, 3H), 1.78 (s, 3H), 4.30 (q, 2H), 6.78 (m, 1H), 6.89 (m, 2H), 7.11 (m, 3H), 7.27 (m, 1H), 7.38 (m, 1H), 8.21 (s, 1H).

EXAMPLE 92

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 32 and 3-chloroaniline following the procedure of Example 49.

LRMS: m/Z 386 $(M+1)^+$

Retention Time: 9.5 min

EXAMPLE 93

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(3-nitrophenyl)pyridazin-3(2*H*)-one

Obtained (83 %) from 5-acetyl-2-ethyl-4-nitro-6-(3-nitrophenyl)pyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-chloroaniline following the procedure of Example 49.

m.p. 173.0-174.2°C

$\delta(CDCl_3)$: 1.46 (t, 3H), 1.81 (s, 3H), 4.31 (q, 2H), 6.99 (d, 1H), 7.09 (s, 1H), 7.17 (m, 1H), 7.27 (m, 1H), 7.60 (m, 2H), 8.18 (s, 1H), 8.26 (m, 2H).

EXAMPLES 94-97

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-(3-nitrophenyl)pyridazin-3(2H)-one

4-{[5-Acetyl-2-ethyl-6-(3-nitrophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzoic acid

5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-(3-nitrophenyl)pyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-(naphthalen-1-ylamino)-6-(3-nitrophenyl)pyridazin-3(2H)-one

The title compounds were synthesized from 5-acetyl-2-ethyl-4-nitro-6-(3-nitrophenyl)pyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and the corresponding aniline following the procedure of Example 49. The ESI/MS data and HPLC retention times are summarized in Table 10.

Table 10

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
94	397	9.0
95	423	8.1
96	458	9.5
97	429	9.6

EXAMPLE 98

5-Butyryl-4-[(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

Obtained from the title compound of Preparation 33 and 3-chloroaniline following the procedure of Example 49.

LRMS: m/Z 396 $(M+1)^+$

Retention Time: 10.2 min

EXAMPLE 99

5-Acetyl-4-[(3-chlorophenyl)amino]-6-phenyl-2-propylpyridazin-3(2*H*)-one

Obtained from 5-acetyl-4-nitro-6-phenyl-2-propylpyridazin-3(2*H*)-one (Dal Piaz, V. *et al*, *Drug Design and Discovery*, **1996**, *14*, 53-57) and 3-chloroaniline following the procedure of Example 49.

LRMS: m/Z 382 $(M+1)^+$

Retention Time: 9.8 min

EXAMPLE 100

5-Acetyl-2-butyl-4-[(3-chlorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

Obtained from 5-acetyl-2-butyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V. *et al*, *Drug Design and Discovery*, **1996**, *14*, 53-57) and 3-chloroaniline following the procedure of Example 49.

LRMS: m/Z 396 $(M+1)^+$

Retention Time: 10.3 min

EXAMPLE 101

5-Acetyl-4-[(3-bromophenyl)amino]-2-butyl-6-phenylpyridazin-3(2H)-one

Obtained from 5-acetyl-2-butyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V. *et al*, *Drug Design and Discovery*, **1996**, *14*, 53-57) and 3-bromoaniline following the procedure of Example 49.

LRMS: m/Z 441 $(M+1)^+$

Retention Time: 10.4 min

EXAMPLE 102

5-Acetyl-4-[*N*-(3,5-dichlorophenyl)-*N*-(3-fluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

A mixture of the title compound of Example 3 (50 mg, 0.12 mmol), 3-fluorophenylboronic acid (33 mg, 0.24 mmol), anhydrous cupric acetate (182 mg, 0.18 mmol), triethylamine (0.034 ml, 0.24 mmol) and activated 4A molecular sieves (110 mg) in dry dichloromethane (2 ml) was stirred under the air at room temperature for 3 days. The reaction was filtered and the solvent removed under reduced pressure. The crude was purified by flash column chromatography (SiO_2, CH_2Cl_2-AcOEt) to yield the title compound (216 mg, 99% yield) as a solid.

$\delta(CDCl_3)$: 1.42 (m, 6H), 4.30 (q, 2H), 6.76 (m, 4H), 7.05 (m, 1H), 7.25 (m, 2H), 7.40 (m, 5H).

EXAMPLES 103-107

5-Acetyl-4-[bis(3-fluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[bis(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[bis(3-methylsulphanylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[bis(3-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[bis-(3,5-dichlorophenyl)amino]-2-ethyl-6-phenyl-2*H*-pyridazin-3-one

The title compounds were synthesized from the title compound of Preparation 22 and an excess of the corresponding arylboronic acid following the experimental procedure described in example 1. The ESI/MS data and HPLC retention times are summarized in Table 11.

Table 11

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
103	446	10.0
104	479	10.7
105	502	10.6
106	494	9.0
107	549	22

EXAMPLE 108

methyl 4-{*N*-(5-acetyl-2-ethyl-6-(4-methylsulphinylphenyl)-3-oxo-2,3-dihydropyridazin-4-yl)-*N*-[4-(methoxycarbonyl)phenyl]amino}benzoate

Obtained from the title compound of Preparation 26 and 4-(methoxycarbonyl)phenylboronic acid following the procedure of Example 102.

LRMS: m/Z 588 $(M+1)^+$

Retention Time: 8.4 min

EXAMPLE 109

5-Acetyl-2-cyclopropylmethyl-4-(3,5-difluoro-phenylamino)-6-phenyl-2H-pyridazin-3-one

The title compound was synthesized from the title compound of Preparation 29 and 3,5-difluorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 396 $(M+1)^+$

Retention Time: 9.8 min

EXAMPLE 110

5-Acetyl-4-(3-fluoro-phenylamino)-2-methyl-6-phenyl-2H-pyridazin-3-one

The title compound was synthesized from 5-acetyl-4-amino-2-methyl-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., *Heterocycles*, **1991**, 32, 1173-9) and the corresponding 3-fluorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 338 $(M+1)^+$

Retention Time: 8.5 min

EXAMPLE 111

4-(5-Acetyl-2-methyl-3-oxo-6-phenyl-2,3-dihydro-pyridazin-4-ylamino)-benzoic acid

A mixture of 5-acetyl-4-amino-2-methyl-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., *Heterocycles*, **1991**, *32*, 1173-9) (100 mg, 0.41 mmol), (4-methoxycarbonylphenyl)boronic acid (148 mg, 0.82 mmol), anhydrous cupric acetate (112 mg, 0.61 mmol), triethylamine (0.11 ml, 0.82 mmol) and activated molecular sieves (520 mg, 4 Å) in dry dichloromethane (4 ml) was stirred under air exposure at room temperature for 48 h. The reaction was filtered and the solvent removed under reduced pressure. The resulting residue was purified by flash column cromathography (SiO_2, dichloromethane-ethyl acetate). The product thus obtained was suspended in a 2:3 THF/MeOH mixture (7 ml), LiOH (50 mg, 1.2 mmol) was added and the mixture was stirred at room temperature for 3 days. Then the solvent was removed and the crude product was suspended in water and the solution was acidified with HCl 2N. Then it was extracted with dichloromethane and the combined organic layers were washed with brine and dried on Na_2SO_4. The solvent was removed to yield a product that was purified by preparative HPLC/MS to isolate the title compound.

LRMS: m/Z 364 $(M+1)^+$

Retention Time: 7.5 min

EXAMPLE 112

5-Acetyl-4-(3,5-dichloro-phenylamino)-2,6-diphenyl-2H-pyridazin-3-one

Obtained as a solid (21%) from 5-acetyl-4-amino-2,6-diphenylpyridazin-3(2H)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., *Heterocycles*, **1991**, *32*, 1173-9) and 3,5-dichlorophenylboronic acid following the procedure of example 1.

LRMS: m/Z 452 (M+1)+

δ(DMSO-d6): 1.89 (s, 3H), 7.15 (s, 2H), 7.22 (s, 2H), 7.40 (m, 6H), 7.52 (m, 2H), 7.66 (d, 2H), 9.27 (bs, 1H).

EXAMPLE 113

5-Acetyl-4-(3-fluoro-phenylamino)-2,6-diphenyl-2H-pyridazin-3-one

Obtained as a solid (57%) from 5-acetyl-4-amino-2,6-diphenylpyridazin-3(2H)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., Heterocycles, 1991, 32, 1173-9) and 3-fluorophenylboronic acid following the procedure of example 1.

LRMS: m/Z 401 (M+1)+

δ(DMSO-d6): 1.80 (s, 3H), 6.91 (m, 3H), 7.32 (q, 1H), 7.36 (m, 6H), 7.53 (t, 2H), 7.67 (d, 2H), 9.22 (s, 1H).

EXAMPLE 114

5-Acetyl-4-(naphthalen-1-ylamino)-2,6-diphenyl-2H-pyridazin-3-one

Obtained as a solid (20%) from 5-acetyl-4-amino-2,6-diphenylpyridazin-3(2H)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., Heterocycles, 1991, 32, 1173-9) and 1-naftalenboronic acid following the procedure of example 1.

LRMS: m/Z 433 (M+1)+

δ(DMSO-d6): 1.23 (s, 2H), 7.26-7.56 (m, 11H), 7.73 (dd, 2H), 7.80 (dd, 2H), 7.94 (dd, 1H), 8.03 (dd, 1H), 9.25 (s, 1H).

EXAMPLE 115

5-Acetyl-4-(3,5-difluoro-phenylamino)-2,6-diphenyl-2H-pyridazin-3-one

Obtained as a solid (26%) from 5-acetyl-4-amino-2,6-diphenylpyridazin-3(2H)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., Heterocycles, 1991, 32, 1173-9) and 3,5-difluorophenylboronic acid following the procedure of example 1.

LRMS: m/Z 419 (M+1)+

δ(DMSO-d6): 1.91 (s, 3H), 6.82 (m, 3H), 7.47 (m, 6H), 7.53 (t, 2H), 7.65 (d, 2H), 9.28 (s, 1H).

EXAMPLE 116

5-Acetyl-4-(3-chloro-phenylamino)-2,6-diphenyl-2H-pyridazin-3-one

Obtained as a solid (61%) from 5-acetyl-4-amino-2,6-diphenylpyridazin-3(2H)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., *Heterocycles*, 1991, 32, 1173-9) and 3-chlorophenylboronic acid following the procedure of example 1.

LRMS: m/Z 417 (M+1)+

δ(DMSO-d6): 1.78 (s, 2H), 7.12 (t, 2H), 7.16 (s, 1H), 7.25 (t, 1H), 7.35 (m, 6H), 7.54 (t, 2H), 7.67 (d, 2H), 9.22 (s, 1H).

EXAMPLE 117

4-(3-Chloro-phenylamino)-2-ethyl-6-phenyl-5-(1-phenyl-methanoyl)pyridazin-2H-one

The title compound was synthesized from the title compound of Preparation 35 and 3,5-difluorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 396 $(M+1)^+$

Retention Time: 9.8 min

EXAMPLE 118

5-[(3-Chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carbaldehyde

The title compound was synthesized from the title compound of Preparation 36 and 3-chlorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 354 $(M+1)^+$

Retention Time: 9.9 min

EXAMPLE 119

Methyl 5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

The title compound was synthesized from the title compound of Preparation 39 and 3-chlorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 384 $(M+1)^+$

Retention Time: 9.6 min

EXAMPLE 120

4-[(3-Chlorophenyl)amino]-2-ethyl-6-phenyl-5-(3-phenylpropanoyl)pyridazin-3(2H)-one

Obtained as a solid (21%) from the title compound of Preparation 43 and 3-chlorophenylboronic acid following the procedure of Example 1.

$\delta(CDCl_3)$: 1.44 (t, 3H), 2.20 (t, 2H), 2.35 (t, 2H), 4.30 (q, 2H), 6.74 (d, 2H), 7.00-7.45 (m, 12H), 8.03 (s, 1H).

EXAMPLE 121

4-[(3,5-Dichlorophenyl)amino]-2-ethyl-6-phenyl-5-(3-phenylpropanoyl)pyridazin-3(2H)-one

Obtained as a solid (36%) from the title compound of Preparation 43 and 3,5-dichlorophenylboronic acid following the procedure of Example 1.

$\delta(CDCl_3)$: 1.44 (t, 3H), 2.37 (m, 4H), 4.29 (q, 2H), 6.59 (m, 2H), 6.76 (m, 2H), 6.9 (s, 2H), 7.08-7.18 (m, 3H), 7.35-7.44 (m, 3H), 8.07 (s, 1H).

EXAMPLE 122

3-{[2-Ethyl-3-oxo-6-phenyl-5-(3-phenylpropanoyl)-2,3-dihydropyridazin-4-yl]amino}benzonitrile

Obtained as a solid (56%) from the title compound of Preparation 43 and 3-cyanophenylboronic acid following the procedure of Example 1.

$\delta(CDCl_3)$: 1.43 (t, 3H), 2.36 (m, 4H), 4.28 (q, 2H), 6.76 (m, 2H), 6.76 (m, 2H), 7.11-7.17 (m, 4H), 7.39-7.45 (m, 8H), 8.33 (s, 1H).

EXAMPLE 123

4-{[2-Ethyl-3-oxo-6-phenyl-5-(3-phenylpropanoyl)-2,3-dihydropyridazin-4-yl]amino}benzoic acid

Obtained as a solid from the title compound of Preparation 43 following the experimental procedure of Example 111.

LRMS: m/Z 468 $(M+1)^+$

Retention Time: 9.5 min

EXAMPLE 124

4-[(3-Chlorophenyl)amino]-2-ethyl-6-phenyl-5-(3-thien-3-ylpropanoyl)pyridazin-3(2H)-one

Obtained as a solid (33%) from the title compound of Preparation 44 and 3-chlorophenylboronic acid following the experimental procedure of Example 1.

LRMS: m/Z 464 $(M+1)^+$

Retention Time: 10.7 min

EXAMPLE 125

4-[(3-Chlorophenyl)amino]-2-ethyl-6-phenyl-5-(3-pyridin-3-ylpropanoyl)pyridazin-3(2H)-one

Obtained as a solid (30%) from the title compound of Preparation 45 and 3-chlorophenylboronic acid following the experimental procedure of Example 1.

LRMS: m/Z 459 $(M+1)^+$

Retention Time: 8.1 min

EXAMPLE 126

5-Acetyl-2-benzyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2H)-one

Obtained as a solid from the title compound of Preparation 28 and 1-naphthylboronic acid following the experimental procedure of Example 1.

LRMS: m/Z 446 $(M+1)^+$

Retention Time: 10.4 min

EXAMPLE 127

4-[(5-Acetyl-2-benzyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

Obtained as a solid from the title compound of Preparation 28 following the experimental procedure of Example 111.

LRMS: m/Z 440 $(M+1)^+$

Retention Time: 8.1 min

EXAMPLE 128-129

5-Acetyl-4-[(3,5-difluorophenyl)amino]-6-phenyl-2-(pyridin-4-ylmethyl) pyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-6-phenyl-2-(pyridin-4-ylmethyl) pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 30 and the corresponding boronic acid following the experimental procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 12.

Table 12

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
128	433	8.3
129	431	8.5

EXAMPLE 130

4-[(5-Acetyl-3-oxo-2,6-diphenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

Obtained as a solid from 5-acetyl-4-amino-2,6-diphenylpyridazin-3(2H)-one (Dal Piaz, V., Ciciani, G, Giovannoni, M.P., *Heterocycles*, **1991**, *32*, 1173-9) following the experimental procedure of Example 111.

LRMS: m/Z 426 $(M+1)^+$

Retention Time: 8.7 min

EXAMPLE 131-133

5-Acetyl-2-(cyclopropylmethyl)-4-[(2-fluorophenyl)amino]-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-phenylpyridazin-3(2H)-one

5-Acetyl-2-(cyclopropylmethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-phenylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 29 and the corresponding boronic acid following the experimental procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 13.

Table 13

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
131	378	9.5
132	394	9.9
133	390	8.6

EXAMPLE 134

3-{[5-Acetyl-2-(cyclopropylmethyl)-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

Obtained as a solid (40%) from the title compound of Preparation 29 and 3-cyanophenylboronic acid following the procedure of Example 1.

m.p. 212.9- 214.0°C.

δ(DMSO-d_6): 0.42-0.53 (m, 4H), 1.33 (m, 1H), 1.82 (s, 3H), 4.02 (d, 2H), 7.34-7.46 (m, 9H), 9.17 (m, 1H).

EXAMPLE 135

4-{[5-Acetyl-2-(cyclopropylmethyl)-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl]amino}benzoic acid

Obtained as a solid (29%) from the title compound of Preparation 29 following the procedure of Example 111.

m.p. 250.7- 251.6°C.

δ(DMSO-d_6): 0.43-0.53 (m, 4H), 1.33 (m, 1H), 1.85 (s, 3H), 4.02 (d, 2H), 7.05 (d, 2H), 7.33 (m, 2H), 7.42 (m, 3H), 7.79 (d, 2H), 9.21 (s, 1H), 12.8 (bs, 1H).

EXAMPLE 136

5-Acetyl-2-isopropyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2H)-one

Obtained as a solid (23%) from the title compound of Preparation 47 and 1-naphthaleneboronic acid following the procedure of Example 1.

m.p. 246.3- 246.9°C.

δ($CDCl_3$): 1.31 (s, 3H), 1.47 (d, 6H), 5.42 (m, 1H), 7.22 (m, 1H), 7.35 (m, 6H), 7.55 (m, 2H), 7.75 (d, 1H), 7.87 (m, 1H), 8.01 (d, 1H), 8.19 (s, 1H).

EXAMPLE 137

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-isopropyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid (54%) from the title compound of Preparation 47 and 3,5-difluorophenylboronic acid following the procedure of Example 1.

m.p. 200.9- 201.6°C.

δ($CDCl_3$): 1.43 (d, 6H), 1.82 (s, 3H), 5.32 (m, 1H), 6.56 (m, 3H), 7.42 (m, 5H), 8.20 (s, 1H).

EXAMPLE 138

5-Acetyl-4-[(3-fluorophenyl)amino]-2-isopropyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid (41%) from the title compound of Preparation 47 and 3-fluorophenylboronic acid following the procedure of Example 1.

m.p. 173.1- 173.5°C.

δ($CDCl_3$): 1.43 (d, 6H), 1.76 (s, 3H), 5.34 (m, 1H), 6.76 (m, 1H), 6.86 (m, 2H), 7.22 (m, 1H), 7.38 (m, 5H), 8.17 (s, 1H).

EXAMPLE 139

5-Acetyl-4-[(3-chlorophenyl)amino]-2-isopropyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid (80%) from the title compound of Preparation 47 and 3-chlorophenylboronic acid following the procedure of Example 1.

m.p. 191.7- 192.2°C.

δ($CDCl_3$): 1.43 (d, 6H), 1.75 (s, 3H), 5.34 (m, 1H), 6.96 (m, 1H), 7.03 (m, 1H), 7.15 (m, 1H), 7.25 (m, 1H), 7.38 (m, 5H), 8.17 (s, 1H).

EXAMPLE 140

5-Acetyl-4-[(3,5-dichlorophenyl)amino]-2-isopropyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid (79%) from the title compound of Preparation 47 and 3,5-dichlorophenylboronic acid following the procedure of Example 1.

m.p. 201.1- 202.3°C.

δ($CDCl_3$): 1.43 (d, 6H), 1.79 (s, 3H), 5.35 (m, 1H), 6.93 (s, 2H), 7.13 (s, 1H), 7.41 (m, 5H), 8.21 (s, 1H).

EXAMPLE 141

4-[(5-Acetyl-2-isopropyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

Obtained as a solid (23%) from the title compound of Preparation 47 following the procedure of Example 111.

m.p. 266.6- 267.5°C.

δ(DMSO-d_3): 1.34 (d, 6H), 1.86 (s, 3H), 5.23 (m, 1H), 7.03 (d, 2H), 7.32 (m, 2H), 7.42 (m, 3H), 7.79 (d, 2H), 9.17 (s, 1H), 12.71 (s, 1H).

EXAMPLE 142-145

5-Acetyl-4-[(2-fluorophenyl)amino]-2-isopropyl-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-2-isopropyl-6-phenylpyridazin-3(2H)-one

3-[(5-Acetyl-2-isopropyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

5-Acetyl-4-{[4-(hydroxymethyl)phenyl]amino}-2-isopropyl-6-phenylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 47 and the corresponding boronic acid following the experimental procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 14.

Table 14

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
142	366	9.6
143	382	10.0

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
144	373	9.2
145	378	8.6

EXAMPLE 146-150

5-Acetyl-4-[(2-fluorophenyl)amino]-2-(2-hydroxyethyl)-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-phenylpyridazin-3(2H)-one

3-{[5-Acetyl-2-(2-hydroxyethyl)-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-Acetyl-2-(2-hydroxyethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-phenylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 49 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 15.

Table 15

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
146	368	7.8
147	384	8.3
148	375	7.5
149	380	6.5
150	384	8.5

EXAMPLE 151-155

5-Acetyl-6-(3-fluorophenyl)-4-[(2-fluorophenyl)amino]-2-(2-hydroxyethyl)pyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-6-(3-fluorophenyl)-2-(2-hydroxyethyl)pyridazin-3(2H)-one

3-{[5-Acetyl-6-(3-fluorophenyl)-2-(2-hydroxyethyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-Acetyl-6-(3-fluorophenyl)-2-(2-hydroxyethyl)-4-{[4-(hydroxymethyl)phenyl]amino}pyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-6-(3-fluorophenyl)-2-(2-hydroxyethyl)pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 51 and the corresponding boronic acid following the experimental procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 16.

Table 16

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
151	386	8.1
152	402	8.5
153	393	7.8
154	398	6.8
155	402	8.7

EXAMPLE 156-160

3-{[5-Acetyl-6-(3-chlorophenyl)-2-(cyclopropylmethyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzamide

5-Acetyl-6-(3-chlorophenyl)-2-(cyclopropylmethyl)-4-{[4-(hydroxymethyl)phenyl]amino}pyridazin-3(2H)-one

3-{[5-Acetyl-6-(3-chlorophenyl)-2-(cyclopropylmethyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-Acetyl-6-(3-chlorophenyl)-2-(cyclopropylmethyl)-4-[(2-fluorophenyl)amino]pyridazin-3(2H)-one

5-Acetyl-6-(3-chlorophenyl)-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 53 and the corresponding aniline following the experimental procedure of Example 49. The mixture was stirred at room temperature overnight. The ESI/MS data and HPLC retention times are summarized in Table 17.

Table 17

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
156	437	9.0
157	424	9.3
158	419	9.8
159	412	10.2
160	429	10.6

EXAMPLE 161-162

3-{[5-Acetyl-2-(cyclopropylmethyl)-6-(3-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzamide

5-Acetyl-2-(cyclopropylmethyl)-6-(3-fluorophenyl)-4-{[4-(hydroxymethyl)phenyl]amino}pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 55 and the corresponding aniline following the experimental procedure of Example 49. The mixture was stirred at room temperature overnight. The ESI/MS data and HPLC retention times are summarized in Table 18.

Table 18

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
161	421	8.4
162	408	8.8

EXAMPLE 163-168

3-{[5-Acetyl-6-(3-fluorophenyl)-2-isopropyl-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzamide

5-Acetyl-6-(3-fluorophenyl)-4-{[4-(hydroxymethyl)phenyl]amino}-2-isopropylpyridazin-3(2H)-one

3-{[5-Acetyl-6-(3-fluorophenyl)-2-isopropyl-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-Acetyl-6-(3-fluorophenyl)-4-[(2-fluorophenyl)amino]-2-isopropylpyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-6-(3-fluorophenyl)-2-isopropylpyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-6-(3-fluorophenyl)-2-isopropylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 57 and the corresponding aniline following the experimental procedure of Example 49. The mixture was stirred at room temperature overnight. The ESI/MS data and HPLC retention times are summarized in Table 19.

Table 19

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
163	409	8.4
164	396	8.8
165	391	9.3
166	383	9.7
167	400	10.1
168	400	10.1

EXAMPLE 169-170

3-{[5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzonitrile

3-{[5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzamide

The title compounds were synthesized from the title compound of Preparation 59 and the corresponding aniline following the experimental procedure of Example 49. The mixture was stirred at room temperature overnight. The ESI/MS data and HPLC retention times are summarized in Table 20.

Table 20

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
169	403	9.4
170	421	8.4

EXAMPLE 171-175

3-{[5-Acetyl-6-(3-chlorophenyl)-2-ethyl-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzamide

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}pyridazin-3(2H)-one

3-{[5-Acetyl-6-(3-chlorophenyl)-2-ethyl-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(2-fluorophenyl)amino]pyridazin-3(2H)-one

5-Acetyl-6-(3-chlorophenyl)-4-[(2-chlorophenyl)amino]-2-ethylpyridazin-3(2H)-one

The title compounds were synthesized from 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and the corresponding aniline following the experimental procedure of Example 49. The mixture was stirred at room temperature overnight. The ESI/MS data and HPLC retention times are summarized in Table 21.

Table 21

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
171	411	8.3
172	398	8.6
173	393	9.3
174	386	9.6
175	403	10.1

EXAMPLE 176

5-Acetyl-2-ethyl-6-(3-fluorophenyl)-4-{[4-(hydroxymethyl)phenyl]amino}pyridazin-3(2H)-one

Obtained (50 %) from the title compound of Preparation 32 and 4-aminophenylmethanol following the procedure of Example 49. The mixture was stirred at room temperature overnight and the final product was purified by flash column chromatography (SiO_2, hexane-ethyl acetate)

m.p. 161.0-162.1

$\delta(CDCl_3)$: 1.44 (t, 3H), 1.73 (s, 3H), 4.29 (q, 2H), 4.67 (s, 2H), 7.10 (m, 5H), 7.33 (m, 3H), 8.20 (s, 1H).

EXAMPLE 177-180

3-{[5-Acetyl-2-ethyl-6-(3-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzamide

3-{[5-Acetyl-2-ethyl-6-(3-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-Acetyl-2-ethyl-6-(3-fluorophenyl)-4-[(2-fluorophenyl)amino]pyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 32 and the corresponding aniline following the experimental procedure of Example 49. The mixture was stirred at room temperature overnight. The ESI/MS data and HPLC retention times are summarized in Table 22.

Table 22

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
177	395	7.7
178	377	8.8
179	370	9.1
180	386	9.5

EXAMPLE 181

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-{[4-(hydroxymethyl)phenyl]amino}pyridazin-3(2H)-one

Obtained (43 %) from the title compound of Preparation 31 and 4-aminophenylmethanol following the procedure of Example 49. The mixture was stirred at room temperature overnight and the final product was purified by flash column chromatography (SiO_2, hexane-ethyl acetate)

m.p. 154.3-156.0

$\delta(CDCl_3)$: 1.44 (t, 3H), 1.71 (s, 3H), 4.29 (q, 2H), 4.67 (s, 2H), 7.08 (m, 4H), 7.33 (m, 4H), 8.16 (s, 1H).

EXAMPLE 182

4-{[5-Acetyl-2-ethyl-6-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzonitrile

Obtained (80 %) from the title compound of Preparation 31 and 4-aminobenzonitrile following the procedure of Example 49. The mixture was stirred at room temperature overnight.

m.p. 207.3-208.4

$\delta(CDCl_3)$: 1.44 (t, 3H), 1.86 (s, 3H), 4.29 (q, 2H), 7.06-7.16 (m, 4H), 7.40 (m, 1H), 7.57 (m, 1H), 7.59 (m, 1H), 7.70 (m, 1H), 8.55 (s, 1H).

EXAMPLE 183-186

3-{[5-Acetyl-2-ethyl-6-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzamide

3-{[5-Acetyl-2-ethyl-6-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(2-fluorophenyl)amino]pyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-(4-fluorophenyl)pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 31 and the corresponding aniline following the experimental procedure of Example 49. The mixture was stirred at room temperature overnight. The ESI/MS data and HPLC retention times are summarized in Table 23.

Table 23

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
183	395	7.6
184	377	8.7
185	370	9.0
186	386	9.4

EXAMPLE 187

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(1-naphthyl)pyridazin-3(2H)-one

Obtained as a solid (83%) from the title compound of Preparation 63 and 3-chlorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 418 $(M+1)^+$

Retention Time: 10.0 min

EXAMPLES 188-227

5-Acetyl-4-[(2,4-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(3,4-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2-chloro-6-methylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(5-fluoro-2-methylphenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(2-methyl-5-nitrophenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2,3-dimethylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2,6-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2,5-dimethylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2,5-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(2-fluoro-5-nitrophenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(3-fluoro-4-methylphenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(3,4-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2-bromophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2,3-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(5-chloro-2-methylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2-chloro-5-methylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-3-methylbenzoic acid
5-Acetyl-4-[(2,4-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-2-chlorobenzoic acid
5-Acetyl-4-[(2-chloro-5-nitrophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(7-hydroxy-1-naphthyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(2-hydroxy-4-methylphenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(2-hydroxy-4-nitrophenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(2-hydroxy-5-methylphenyl)amino]-6-phenylpyridazin-3(2H)- one
5-Acetyl-2-ethyl-4-[(2-hydroxy-5-nitrophenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(2-methoxy-4-nitrophenyl)amino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-6-phenyl-4-{[4-(trifluoromethoxy)phenyl]amino}pyridazin-3(2H)-one
5-Acetyl-4-[(3-ethoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-[(2-methoxy-5-methylphenyl)amino]-6-phenylpyridazin-3(2H)-one
4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-1-naphthonitrile

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-5-nitrobezoic acid

5-Acetyl-2-ethyl-4-[(3-mercaptophenyl)amino]-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(2-chloro-5-methoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-3-methoxybenzoic acid

5-Acetyl-2-ethyl-4-{[3-(1-hydroxyethyl)phenyl]amino}-6-phenylpyridazin-3(2H)- one

5-Acetyl-2-ethyl-4-{[3-(hydroxymethyl)phenyl]amino}-6-phenylpyridazin-3(2H)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-3-hydroxybenzoic acid

5-Acetyl-2-ethyl-4-{[4-(1-hydroxyethyl)phenyl]amino}-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(3,5-dimethoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

The title compounds were synthesized from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and the corresponding aniline following the procedure of Example 49. The ESI/MS data and HPLC retention times are summarized in Table 24.

Table 24

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
188	370	9.1
189	403	9.9
190	386	9.5
191	382	9.7
192	366	9.4
193	393	9.3
194	362	9.6
195	370	9.0
196	362	9.7
197	370	9.1
198	397	9.2
199	366	9.4
200	370	9.1
201	413	9.5
202	370	9.2
203	382	9.9
204	382	9.8
205	392	8.4

206	403	10.0
207	412	8.4
208	413	9.6
209	400	8.9
210	364	8.7
211	395	8.7
212	364	8.7
213	395	8.6
214	409	9.3
215	418	9.8
216	378	9.4
217	378	9.4
218	409	9.4
219	423	8.8
220	366	8.5
221	398	9.5
222	408	8.4
223	378	8.2
224	364	7.8
225	394	7.8
226	378	8.2
227	394	9.1

EXAMPLE 228

5-Acetyl-4-[(2,6-dimethylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2,6-dimethylaniline following the procedure of Example 49 (5h at room temperature, 58% yield).

m.p. 187.8-188.9°C.

$\delta(CDCl_3)$: 1.36 (s, 3H), 1.46 (t, 3H), 2.23 (s, 6H), 4.30 (q, 2H), 7.05 (m, 3H), 7.34 (m, 5H), 7.68 (s, 1H).

EXAMPLE 229

5-Acetyl-2-ethyl-4-{[4-(2-hydroxyethyl)phenyl]amino}-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2-(4-aminophenyl)ethanol following the procedure of Example 49 (3.5 h at room temperature, flash column chromatography purification, 71% yield).

m.p. 145.8-146.6°C.

δ($CDCl_3$): 1.42 (t, 3H), 1.66 (s, 3H), 2.84 (m, 2H), 3.82 (m, 2H), 4.30 (q, 2H), 7.02 (d, 2H), 7.17 (d, 2H), 7.38 (m, 5H), 8.18 (s, 1H).

EXAMPLE 230

5-Acetyl-2-ethyl-4-[(4-nitrophenyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-nitrophenylamine following the procedure of Example 49 (69 h at room temperature, 73% yield).

m.p. 209.8-210.7°C.

δ(DMSO-d6): 1.34 (t, 3H), 2.04 (s, 3H), 4.19 (q, 2H), 7.04 (d, 2H), 7.39 (m, 2H), 7.44 (m, 3H), 8.08 (d, 2H), 9.46 (s, 1H).

EXAMPLE 231

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-aminobenzonitrile following the procedure of Example 49 (20 h at room temperature, 80% yield).

m.p. 204.1-204.5°C.

δ($CDCl_3$): 1.44 (t, 3H), 1.87 (s, 3H), 4.30 (q, 2H), 7.06 (d, 2H), 7.44 (m, 5H), 7.58 (d, 2H), 8.61 (s, 1H).

EXAMPLE 232

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzamide

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-aminobenzamide following the procedure of Example 49 (1 h at room temperature, 90% yield).

m.p. 215.8-216.7°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.65 (s, 3H), 4.18 (q, 2H), 7.19 (d, 1H), 7.31 (m, 1H), 7.40 (m, 6H), 7.51 (s, 1H), 7.58 (d, 1H), 7.87 (s, 1H), 9.05 (s, 1H).

EXAMPLE 233

5-Acetyl-2-ethyl-4-{[2-(hydroxymethyl)phenyl]amino}-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and (2-aminophenyl)methanol following the procedure of Example 49 (1.5 h at room temperature, 48% yield).

m.p. 152.8-153.9°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.55 (s, 3H), 4.17 (q, 2H), 4.52 (d, 2H), 5.36 (t, 1H), 6.93 (m, 1H), 7.11 (m, 2H), 7.28 (m, 2H), 7.39 (m, 4H), 8.70 (s, 1H).

EXAMPLE 234

2-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzamide

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2-aminobenzamide following the procedure of Example 49 (2 h at room temperature, 61% yield).

m.p. 185.5-186.8°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.79 (s, 3H), 4.17 (q, 2H), 6.88 (d, 1H), 7.03 (t, 1H), 7.26 (t, 1H), 7.35 (m, 2H), 7.44 (m, 3H), 7.63 (m, 2H), 8.14 (s, 1H), 10.08 (s, 1H).

EXAMPLE 235

2-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzene sulfonamide

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2-aminobenzenesulfonamide following the procedure of Example 49 (96 h at room temperature, flash column chromatography purification, 35% yield).

m.p. 120.0-122.7°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.84 (s, 3H), 4.19 (q, 2H), 7.01 (d, 1H), 7.20 (t, 1H), 7.37 (m, 2H), 7.41 (m, 4H), 7.70 (s, 2H), 7.81 (d, 1H), 8.74 (s, 1H).

EXAMPLE 236

2-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2-aminobenzonitrile following the procedure of Example 49 (6 days at room temperature, 16% yield).

m.p. 169.7-170.2°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.69 (s, 3H), 4.18 (q, 2H), 7.30 (m, 4H), 7.41 (m, 3H), 7.54 (t, 1H), 7.76 (d, 1H), 9.26 (s, 1H).

EXAMPLE 237

5-Acetyl-4-[(2,6-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2,6-dichlorophenylamine following the procedure of Example 49 (6 days at 60°C, 12% yield).

m.p. 233.6-234.4°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.55 (s, 3H), 4.17 (q, 2H), 7.31 (m, 3H), 7.41 (m, 3H), 7.48 (m, 2H), 9.03 (s, 1H).

EXAMPLE 238

5-Acetyl-2-ethyl-4-[(2-nitrophenyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2-nitrophenylamine following the procedure of Example 49 (4 days at 50°C, flash column chromatography purification, 50% yield).

m.p. 151.2-153.0°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.87 (s, 3H), 4.17 (q, 2H), 7.21 (m, 2H), 7.40 (m, 2H), 7.47 (m, 3H), 7.58 (t, 1H), 8.07 (d, 1H), 9.46 (s, 1H).

EXAMPLE 239

5-Acetyl-4-[(5-chloro-2-hydroxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2-amino-4-chlorophenol following the procedure of Example 49 (2h at room temperature, 91% yield).

m.p. 239.4-240.7°C.

δ(DMSO-d6): 1.31 (t, 3H), 1.60 (s, 3H), 4.14 (q, 2H), 6.75 (m, 1H), 7.00 (m, 2H), 7.27 (m, 2H), 7.40 (m, 3H), 8.50 (s, 1H), 9.99 (s, 1H).

EXAMPLE 240

5-Acetyl-4-[(3-chloro-4-hydroxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-amino-2-chlorophenol following the procedure of Example 49 (2h at room temperature, 80% yield).

m.p. 207.1-207.6°C.

δ(DMSO-d6): 1.31 (t, 3H), 1.62 (s, 3H), 4.14 (q, 2H), 6.83 (m, 2H), 7.06 (m, 1H), 7.25 (m, 2H), 7.38 (m, 3H), 8.76 (s, 1H), 10.13 (s, 1H).

EXAMPLE 241

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzenesulfonamide

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-aminobenzenesulfonamide following the procedure of Example 49 (3 h at room temperature, 87% yield).

m.p. 192.0-194.2°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.74 (s, 3H), 4.18 (q, 2H), 7.17 (d, 1H), 7.33 (m, 4H), 7.45 (m, 6H), 9.14 (s, 1H).

EXAMPLE 242

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-1-naphthoic acid

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-aminonaphthalene-1-carboxylic ac
Id following the procedure of Example 49 (24 h at room temperature, 54% yield).

m.p. 258.1-260.2°C.

δ(DMSO-d6): 1.36 (t, 3H), 1.41 (s, 3H), 4.21 (q, 2H), 7.24 (m, 3H), 7.40 (m, 3H), 7.66 (m, 2H), 8.02 (d, 1H), 8.16 (d, 1H), 8.93 (d,1H), 9.19 (s, 1H), 13.05 (bs, 1H).

EXAMPLE 243

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-4-methoxybenzamida

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-amino-4-methoxybenzamide following the procedure of Example 49 (1 h at room temperature, 66% yield).

m.p. 246.1-247.5°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.53 (s, 3H), 3.80 (s, 3H), 4.17 (q, 2H), 7.04 (d, 1H), 7.1-7.5 (m, 6H), 7.59 (s, 1H), 7.7-7.8 (m, 2H), 8.52 (s, 1H).

EXAMPLE 244

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-2-methoxybenzoic acid

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-amino-2-methoxybenzoic acid following the procedure of Example 49 (30 h at room temperature, 83% yield).

m.p. 210.9-211.8°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.88 (s, 3H), 3.71 (s, 3H), 4.18 (q, 2H), 6.62 (d, 1H), 6.74 (s, 1H), 7.2-7.5 (m, 5H), 7.57 (d, 1H), 9.14 (s, 1H), 12.28 (bs, 1H).

EXAMPLE 245

5-acetyl-2-ethyl-4-[(3-fluoro-4-hydroxyphenyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-amino-2-fluorophenol following the procedure of Example 49 (1 h at room temperature, 83% yield).

m.p. 241.8-242.6°C.

δ(DMSO-d6): 1.32 (t, 3H), 1.65 (s, 3H), 4.15 (q, 2H), 6.71 (t, 1H), 6.80 (t, 1H), 6.93 (d, 1H), 7.26 (m, 2H), 7.39 (m, 3H), 8.78 (s, 1H), 9.81 (s, 1H).

EXAMPLE 246

5-acetyl-2-ethyl-4-[(5-fluoro-2-hydroxyphenyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2-amino-4-fluorophenol following the procedure of Example 49 (24 h at room temperature, 88% yield).

m.p. 190.1-190.5°C.

δ(DMSO-d6): 1.19 (t, 3H), 1.49 (s, 3H), 4.02 (q, 2H), 6.6-6.8 (m, 3H), 7.0-7.4 (m, 5H), 8.36 (s, 1H), 9.56 (s, 1H).

EXAMPLE 247

5-Acetyl-2-ethyl-4-[(6-hydroxy-1-naphthyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 5-amino-2-naphthol following the procedure of Example 49 (1.5 h at room temperature, 76% yield).

m.p. 235.5-236.7°C.

δ(DMSO-d6): 1.21 (s, 3H), 1.37 (t, 3H), 4.21 (q, 2H), 6.98 (d, 1H), 7.0-7.4 (m, 8H), 7.54 (d, 1H), 7.83 (d, 1H), 8.96 (s, 1H), 9.84 (s, 1H).

EXAMPLE 248

5-Acetyl-2-ethyl-4-[(3-fluoro-2-methylphenyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-fluoro-2-methylaniline following the procedure of Example 49 (1 h at room temperature, 68% yield).

m.p. 189.3-190.6°C.

δ(DMSO-d6): 1.35 (t, 3H), 1.46 (s, 3H), 2.11 (s, 3H), 4.18 (q, 2H), 6.89 (d, 1H), 7.0-7.2 (m, 3H), 7.2-7.5 (m, 5H), 8.74 (s, 1H).

EXAMPLE 249

5-acetyl-2-ethyl-4-[(2-hydroxy-1-naphthyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 1-amino-2-naphthol following the procedure of Example 49 (4 h at room temperature, 52% yield).

m.p. 231.2-235.2°C.

δ(DMSO-d6): 1.15 (s, 3H), 1.37 (t, 3H), 4.21 (q, 2H), 7.09 (d, 1H), 7.2-7,5 (m, 7H), 7.6-7.8 (m, 3H), 8.54 (s, 1H), 9.95 (s, 1H).

EXAMPLE 250

5-Acetyl-2-ethyl-4-[(5-hydroxy-1-naphthyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 5-amino-1-naphthol following the procedure of Example 49 (24 h at room temperature, 24% yield).

m.p. 234.8-235.9°C.

δ(DMSO-d6): 1.18 (s, 3H), 1.37 (t, 3H), 4.21 (q, 2H), 6.89 (d, 2H), 7.2-7.5 (m, 8H), 8.0 (d, 1H), 8.94 (s, 1H), 10.22 (s, 1H).

EXAMPLE 251

4-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-3-fluorobenzoic acid

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-amino-3-fluorobenzenecarboxylic acid following the procedure of Example 49 (6 days at room temperature, 78% yield).

m.p. 238.1-240.9°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.78 (s, 3H), 4.17 (q, 2H), 7.26 (t, 1H), 7.3-7.5 (m, 5H), 7.60 (d, 1H), 7.66 (d, 1H), 9.07 (s, 1H), 13.14 (bs, 1H).

EXAMPLE 252

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-N,N-dimethylbenzamide

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and and 3-amino-*N*,*N*-dimethyl-benzamide following the procedure of Example 49 (24 h at room temperature, 80% yield).

m.p. 190.1-190.5°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.72 (s, 3H), 2.89 (s, 3H), 2.94 (s, 3H), 4.17 (q, 2H), 7.0-7.2 (m, 3H), 7.2-7.5 (m, 6H), 9.05 (s, 1H).

EXAMPLE 253

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-N-methylbenzamide

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-aminobenzoylmethylamide following the procedure of Example 49 (24 h at room temperature, 74% yield).

m.p. 195.1-195.6°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.66 (s, 3H), 2.74 (d, 3H), 4.18 (q, 2H), 7.20 (d, 1H), 7.2-7.6 (m, 8H), 8.35 (d, 1H), 9.06 (s, 1H).

EXAMPLE 254

5-Acetyl-2-ethyl-4-[(4-nitro-1-naphthyl)amino]-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 1-amino-4-nitronaphthalene following the procedure of Example 49 (2 h microwave oven, 11% yield).

m.p. 185.2-185.8°C.

δ(DMSO-d6): 1.37 (t, 3H), 1.71 (s, 3H), 4.22 (q, 2H), 7.18 (m, 1H), 7.3-7.5 (m, 5H), 7.73 (t, 1H), 7.84 (t, 1H), 8.25 (d, 1H), 8.35 (d, 1H), 8.53 (d, 1H), 9.39 (s, 1H).

EXAMPLE 255

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-2-fluorobenzoic acid

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-amino-2-fluorobenzoic acid following the procedure of Example 49 (20 h at room temperature, 72% yield).

m.p. 235.7-236.2°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.96 (s, 3H), 4.18 (q, 2H), 6.8-6.9 (m, 2H), 7.3-7.5 (m, 5H), 7.71 (t, 1H), 9.27 (s, 1H), 12.89 (s, 1H).

EXAMPLE 256

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-3-chlorobenzoic acid

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-amino-3-chlorobenzoic acid following the procedure of Example 49 (15 days at room temperature, 35% yield).

m.p. 197.5-198.2°C.

δ(DMSO-d6): 1.19 (t, 3H), 1.63 (s, 3H), 4.03 (q, 2H), 7.05 (d, 1H), 7.2-7.4 (m, 5H), 7.61 (dd, 1H), 7.76 (d, 1H), 8.69 (s, 1H).

EXAMPLE 257

5-Acetyl-4-[(3-chloro-2-methylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-chloro-2-methylaniline following the procedure of Example 49 (1.5 h at room temperature, 93% yield).

m.p. 219.7-220.5°C.

δ(DMSO-d6): 1.35 (t, 3H), 1.45 (s, 3H), 2.24 (s, 3H), 4.18 (q, 2H), 7.0-7.1 (m, 2H), 7.2-7.5 (m, 6H), 8.81 (s, 1H).

EXAMPLE 258

Methyl 4-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoate

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and methyl 4-aminobenzoate following the procedure of Example 49 (24 h at room temperature, 61% yield).

m.p. 177.8-179.1°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.86 (s, 3H), 3.80 (s, 3H), 7.07 (dd, 2H), 7.3-7.5 (m, 5H), 7.80 (dd, 2H), 9.24 (s, 1H).

EXAMPLE 259

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-5-chloro-2-methoxybenzoic acid

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 4-amino-5-chloro-2-methoxybenzoic acid following the procedure of Example 49 (8 days at 50°, 30% yield).

δ(DMSO-d6): 1.34 (t, 3H), 1.79 (s, 3H), 3.71 (s, 3H), 4.18 (q, 2H), 6.89 (s, 1H), 7.3-7.5 (m, 5H), 7.69 (s, 1H), 8.72 (s, 1H), 12.6-12.8 (bs, 1H).

EXAMPLE 260

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-4-methylbenzamide

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-amino-4-methylbenzamide following the procedure of Example 49 (2 h at room temperature, 78% yield).

m.p. 236.1-237.9°C.

δ(DMSO-d6): 1.36 (t, 3H), 1.37 (s, 3H), 2.27 (s, 3H), 4.19 (q, 2H), 7.2-7.5 (m, 7H), 7.51 (s, 1H), 7.63 (d, 1H), 7.82 (s, 1H), 8.69 (s, 1H).

EXAMPLE 261

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-4-chlorobenzamide

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3-amino-4-chlorobenzamide following the procedure of Example 49 (48 h at room temperature, 27% yield).

m.p. 219.2-220.1°C.

δ(DMSO-d6): 1.34 (t, 3H), 1.58 (s, 3H), 4.18 (q, 2H), 7.3-7.5 (m, 5H), 7.47 (s, 1H), 7.57 (d, 1H), 7.69 (s, 1H), 7.71 (d, 1H), 7.97 (s, 1H), 8.83 (s, 1H).

EXAMPLE 262

5-Acetyl-4-[(4-chloro-1-naphthyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 1-amino-4-chloronaphthalene following the procedure of Example 49 (4 h at room temperature, 80% yield).

m.p. 191.0-192.3°C.

δ(DMSO-d6): 1.29 (s, 3H), 1.38 (t, 3H), 4.22 (q, 2H), 7.2-7.4 (m, 5H), 7.29 (s, 1H), 7.58 (d, 1H), 7.72 (m, 2H), 8.08 (d, 1H), 8.17 (d, 1H), 9.15 (s, 1H).

EXAMPLE 263 LAS37729

5-Acetyl-2-ethyl-6-phenyl-4-[(2,4,6-trifluorophenyl)amino]pyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 2,4,6-trifluoroaniline following the procedure of Example 49 (19 h at 50°, 33% yield).

m.p. 200.2-201.0°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.62 (s, 3H), 4.17 (q, 2H), 7.2-7.5 (m, 7H), 8.71 (s, 1H).

EXAMPLE 264

5-Acetyl-2-ethyl-6-phenyl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one

Obtained as a solid from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* **1997**, *40*, 1417) and 3,4,5-trifluoroaniline following the procedure of Example 49 (16 h at 50°, 56% yield).

m.p. 203.0-203.8°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.85 (s, 3H), 4.17 (q, 2H), 7.00 (dd, 2H), 7.3-7.5 (m, 5H), 9.09 (s, 1H).

EXAMPLE 265

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-4-chlorobenzoic acid

To a stirred solution of 80 mg (0.28 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (2 ml), 3-amino-4-chlorobenzoic acid (95 mg, 0.55 mmol) was added portionwise The resulting mixture was irradiated in microwave oven for three hours at 120°C. The final product was collected by filtration and washed with diethylether to yield the title compound (50 mg, 44 % yield).

m.p. 254.6-255.9°C.

δ(DMSO-d6): 1.36 (t, 3H), 1.62 (s, 3H), 4.17 (q, 2H), 7.31 (m, 2H), 7.42 (m, 3H), 7.59 (d,1H), 7.65 (s, 1H), 7.35 (d, 1H), 8.88 (s, 1H), 13.21 (bs, 1H).

EXAMPLE 266

5-Acetyl-4-{[4-(aminomethyl)phenyl]amino}-2-ethyl-6-phenylpyridazin-3(2H)-one

To a stirred solution of 100 mg (0.348 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (6 ml), (4-aminobenzyl)carbamic acid *tert*-butyl ester (Gallo-Rodriguez, C et al *J. Med. Chem.* 1994, 37(5), 636-46) (116 mg, 0.52 mmol) was added portionwise. The resulting mixture was stirred at room temperature for 1 h. The precipitate thus formed was collected by filtration

and washed with diethylether. Then it was solved in dichloromethane (1mL) and trifluoroacetic acid (0.23 mL, 3.03 mmol) was added dropwise. The final mixture was stirred at room temperature for 20 minutes. Some more dichloromethane was added and this solution was washed with saturated K2CO3 solution until pH 6. The organic layer was dried and solvent removed to yield 70 mg (54% yield) of the title compound.

m.p. 138.9-139.3°C.

δ($CDCl_3$): 1.44 (t, 3H), 1.68 (s, 3H), 1.99 (bs, 2H), 3.87 (bs, 2H), 4.30 (q, 2H), 4.17 (q, 2H), 7.03 (d, 2H), 7.25 (d, 2H), 7.34 (m, 5H), 8.21 (s, 1H).

EXAMPLE 267

5-Acetyl-4-{[4-(2-aminoethyl)phenyl]amino}-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained as a solid (84%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) and [2-(4-aminophenyl)-ethyl]-carbamic acid *tert*-butyl ester (Dannhardt, G. Et al *Archiv der Pharmazie* , 2000, 333(8), 267-74) following the procedure of Example 266.

m.p. 71.8-72.5°C.

δ($CDCl_3$): 1.44 (t, 3H), 1.67 (s, 3H), 1.91 (bs, 2H), 2.75 (t, 2H), 2.97 (t, 2H), 4.29 (q, 2H), 7.02 (d, 2H), 7.14 (d, 2H), 7.36 (m, 5H), 8.19 (s, 1H).

EXAMPLE 268

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2H)-one

Obtained as a solid (17%) from the title compound of Preparation 23 and 3-fluorophenylboronic acid following the procedure of Example 1.

m.p. 168.7-169.1°C.

δ(DMSO-d6): 1.33 (t, 3H), 1.80 (s, 3H), 3.34 (s, 3H), 4.17 (q, 2H), 6.87 (m, 3H), 7.26 (m, 5H), 9.06 (s, 1H).

EXAMPLE 269

1-Ethyl-5-[(3-fluorophenyl)amino]-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylic acid

To a stirred solution of the title compound of preparation 65 (0.5 g, 1.43 mmol) in 35 mL of ethanol, ammonium formate (270 mh, 4.27 mmol) and 10% palladium on charcoal (55 mg) were added and the mixture was refluxed for 1 h. The catalyst was filtered off through

a Celite pad and solvent was removed under educed pressure to yield the title compound (0.42 g, 84% yield).

LRMS: m/Z 354 $(M+1)^+$

$\delta(CDCl_3)$: 1.42 (t, 3H), 4.35 (q, 2H), 6.85 (m, 3H), 7.21-7.58 (m, 6H), 8.02 (s, 1H).

EXAMPLE 270

5-[(3-Chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylic acid

A mixture of the title compound of Preparation 64 (1.57 g, 6.1 mmol), 3-chlorophenylboronic acid (1.24 g, 7.9 mmol), anhydrous cupric acetate (1.66 g, 9.15 mmol), triethylamine (1.20 ml, 8.5 mmol) and activated molecular sieves (5 g, 4 Å) in dry dichloromethane (75 ml) was stirred under air exposure at room temperature overnight. The reaction mixture was filtered through a SiO_2 pad and eluted with dichloromethane. The solvent was removed under reduced pressure and the product was purified by column chromatography (SiO2, hexane-ethylacetate). 380mg of the final product (19% yield) were obtained.

LRMS: m/Z 370 $(M+1)^+$

Retention Time: 8.3 min

EXAMPLE 271

Methyl 1-ethyl-5-[(3-fluorophenyl)amino]-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

To a stirred solution of the title compound of example 270 (140 mg, 0.40 mmol) in 6 mL of dry DMF, anhydrous potassium carbonate (157 mg, 0.40 mmol) was added and the mixture was stirred for a while. Finally, methyl iodide (157 mg, 1.11 mmol) was added and the final mixture was stirred at room temperature for 1 hour. Then some water was added until a solid appeared. It was collected by filtration and washed with cold water to yield the title compound (120 mg, 83% yield).

m.p. 187.4-188.3°C.

$\delta(DMSO\text{-}d_6)$: 1.34 (t, 3H), 2.92 (s, 3H), 4.17 (q, 2H), 6.92 (m, 3H), 7.34 (m, 6H), 9.25 (s, 1H).

EXAMPLE 272-274

Isopropyl 5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

Ethyl 5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

The title compounds were synthesized from the title compound of Example 270 and the corresponding alkylating agent following the experimental procedure of Example 271. The ESI/MS data and HPLC retention times are summarized in Table 25.

Table 25

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
272	412	10.4
272	398	10.1

EXAMPLE 274

Benzyl 5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

Obtained (20%) from the title product of Example 270 and benzyl bromide following the experimental procedure of Example 271.

m.p. 181.8-182.4°C.

$\delta(CDCl_3)$: 1.43 (t, 3H), 1.56 (s, 3H), 4.32 (q, 2H), 4.40 (s, 2H), 6.80 (d, 2H), 7.05 (d, 1H), 7.15-7.36 (m, 11H), 7.92 (s, 1H).

The following examples illustrate pharmaceutical compositions according to the present invention and procedure for their preparation.

COMPOSITION EXAMPLE 1

Preparation of tablets

Formulation:

Compound of the present invention	5.0 mg
Lactose	113.6 mg
Microcrystalline cellulose	28.4 mg
Light silicic anhydride	1.5 mg
Magnesium stearate	1.5 mg

Using a mixer machine, 15 g of the compound of the present invention are mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture is subjected to compression moulding using a roller compactor to give a flake-like compressed material. The flake-like compressed material is pulverised using a hammer mill, and the pulverised material is screened through a 20 mesh screen. A 4.5 g portion of light silicic anhydride and 4.5 g of magnesium stearate are added to the screened material and mixed. The mixed product is subjected to a tablet making machine equipped with a die/punch system of 7.5 mm in diameter, thereby obtaining 3,000 tablets each having 150 mg in weight.

COMPOSITION EXAMPLE 2

Preparation of coated tablets

Formulation:

Compound of the present invention	5.0 mg
Lactose	95.2 mg
Corn starch	40.8 mg
Polyvinylpyrrolidone K25	7.5 mg
Magnesium stearate	1.5 mg
Hydroxypropylcellulose	2.3 mg
Polyethylene glycol 6000	0.4 mg
Titanium dioxide	1.1 mg
Purified talc	0.7 mg

Using a fluidised bed granulating machine, 15 g of the compound of the present invention are mixed with 285.6 g of lactose and 122.4 g of corn starch. Separately, 22.5 g of polyvinylpyrrolidone is dissolved in 127.5 g of water to prepare a binding solution. Using a fluidised bed granulating machine, the binding solution is sprayed on the above mixture to give granulates. A 4.5 g portion of magnesium stearate is added to the obtained granulates and mixed. The obtained mixture is subjected to a tablet making machine equipped with a die/punch biconcave system of 6.5 mm in diameter, thereby obtaining 3,000 tablets, each having 150 mg in weight.

Separately, a coating solution is prepared by suspending 6.9 g of hydroxypropylmethylcellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a High Coated, the 3,000 tablets prepared above are coated with the coating solution to give film-coated tablets, each having 154.5 mg in weight.

COMPOSITION EXAMPLE 3

Preparation of capsules

Formulation:

Compound of the present invention	5.0 mg
Lactose monohydrate	200 mg
Colloidal silicon dioxide	2 mg
Corn starch	20 mg
Magnesium stearate	4 mg

25 g of active compound, 1 Kg of lactose monohydrate, 10 g of colloidal silicon dioxide, 100 g of corn starch and 20 g of magnesium stearate are mixed. The mixture is sieved through a 60 mesh sieve, and then filled into 5,000 gelatine capsules.

COMPOSITION EXAMPLE 4

Preparation of a cream

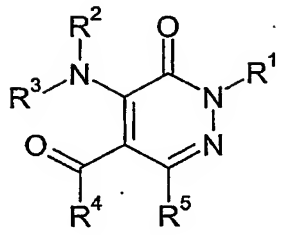
Formulation:

Compound of the present invention	1 %
Cetyl alcohol	3 %
Stearyl alcohol	4 %
Gliceryl monostearate	4 %
Sorbitan monostearate	0.8 %
Sorbitan monostearate POE	0.8 %
Liquid vaseline	5 %
Methylparaben	0.18 %
Propylparaben	0.02 %
Glycerine	15 %
Purified water csp.	100 %

An oil-in-water emulsion cream is prepared with the ingredients listed above, using conventional methods.

CLAIMS

1. A compound of formula (I)



(I)

wherein

R^1 represents:

- a hydrogen atom
- a group selected from acyl, alkoxycarbonyl, carbamoyl, monoalkylcarbamoyl or dialkylcarbamoyl;
- an alkyl group, which is optionally substituted by one or more substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, carbamoyl or mono- or di-alkylcarbamoyl groups;
- or a group of formula

$$-(CH_2)_n-R^6$$

wherein n is an integer from 0 to 4 and R^6 represents:

- a cycloalkyl group;
- an aryl group, which is optionally substituted by one or more substituents selected from halogen atoms and alkyl, hydroxy, alkoxy, alkylenedioxy, alkylthio, amino, mono- or di-alkylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, cyano, trifluoromethyl, difluoromethoxy or trifluoromethoxy groups;
- or a 3- to 7-membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by one or more substituents

selected from halogen atoms and alkyl, hydroxy, alkoxy, alkylenedioxy, amino, mono- or di-alkylamino, nitro, cyano or trifluoromethyl groups;

R^2 represents a substituent selected from R^1 and an alkyl group, which is substituted by a hydroxycarbonyl or an alkoxycarbonyl group.

R^3 and R^5 each independently represent a monocyclic or bicyclic aryl group, which is optionally substituted by one or more substituents selected from:

- halogen atoms;
- alkyl and alkylene groups, which are optionally substituted by one or more substituents selected from halogen atoms and phenyl, hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl or mono- or di-alkylcarbamoyl groups;
- and phenyl, hydroxy, alkylenedioxy, alkoxy, cycloalkyloxy, alkylthio, alkylsulphinyl, amino, mono- or di-alkylamino, acylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido, alkylsulphamido, aminosuphonyl, mono- or di-alkylaminosulphonyl, cyano, difluoromethoxy or trifluoromethoxy groups;

R^4 represents:

- a hydrogen atom;
- a hydroxy, alkoxy, amino, mono- or di-alkylamino group;
- an alkyl group which is optionally substituted by one or more substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl and mono- or di-alkylcarbamoyl groups;
- or a group of formula

$$-(CH_2)_n-R^6.$$

wherein n and R^6 are as defined above.

with the proviso that when R^2 is H and R^3 and R^5 are unsubstituted phenyl, R^1 is not methyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is a hydrogen atom; a straight or branched C_1-C_4 alkyl group, which is optionally substituted by halogen atoms and/or 1 or 2 substituents selected from hydroxy, alkoxy, amino, monalkylamino and dialkylamino groups; or a group of formula $-(CH_2)_n-R^6$, wherein n is an integer from 0 to 4 and R^6 is an optionally substituted phenyl, cycloalkyl or 5- to 6-membered heterocyclic ring comprising at least one nitrogen atom.

3. A compound according to claim 2 wherein R^1 is an unsubstituted straight or branched C_1-C_4 alkyl group, or a group of formula $-(CH_2)_n-R^6$, wherein n is 0 or 1 and R^6 is cyclopropyl, phenyl or pyridyl.

4. A compound according to claim 1 wherein R^2 is a hydrogen atom or a group selected from alkoxycarbonyl; carbamoyl; a straight C_1-C_4 alkyl group, which is optionally substituted by a hydroxy group; or a group of formula $-(CH_2)_n-R^6$, wherein n is 0 and R^6 is a phenyl ring, which is optionally substituted by 1 or 2 substituents selected from halogen, alkyl, acyl, alkoxy, alkylthio and alkoxycarbonyl.

5. A compound according to claim 4 wherein R^2 is a hydrogen atom, an unsubstituted straight C_1-C_4 alkyl group or a phenyl ring, which is optionally substituted by 1 or 2 substituents selected from halogen, alkyl, acyl, alkoxy, alkylthio and alkoxycarbonyl.

6. A compound according to claim 1 wherein R^3 is a phenyl or naphthyl group, which is optionally substituted by 1 or 2 substituents selected from halogen, hydroxy, alkoxy, cycloalkyloxy, alkylthio, cyano, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, acylamino, aminosulphonyl, carbamoyl, trifluoromethoxy, alkylenedioxy, alkyl and alkylene, wherein said alkyl and alkylene groups are optionally substituted by halogen atoms or by a group selected from hydroxy, oxo, phenyl, amino and hydroxycarbonyl.

7. A compound according to claim 1 wherein R^4 is a substituent selected from hydrogen; hydroxy; alkoxy; amino; monoalkylamino; dialkylamino; a straight or branched C_1-C_6 alkyl

group, which is optionally substituted by hydroxy, alkoxy, amino, monoalkylamino or dialkylamino groups; or a group of formula $-(CH_2)_n-R^6$, wherein n is 0, 1 or 2 and R^6 is a phenyl group.

8. A compound according to claim 7 wherein R^4 is a substituent selected from hydrogen, methoxy, unsubstituted straight or branched C_1-C_6 alkyl and phenyl.

9. A compound according to claim 1 wherein R^5 is a phenyl group, which is optionally substituted by 1 or 2 substituents selected from halogen, hydroxy, alkoxy, cycloalkyloxy, alkylthio, alkylsulphinyl, nitro, cyano, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, monalkylcarbamoyl, dialkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido and an optionally substituted straight or branched C_1-C_6 alkyl group.

10. A compound according to claim 9 wherein R^5 is a phenyl group, which is optionally substituted by 1 or 2 substituents selected from halogen, alkoxy, cycloalkyloxy, alkylthio, alkylsulphinyl and nitro.

11. A compound according to claim 1 which is one of:

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3,5-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one.
5-Acetyl-2-ethyl-4-[(3-nitrophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(4-methylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(2-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-{[4-(methylthio)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(4-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-{[4-(dimethylamino)phenyl]amino}-2-ethyl-6-phenylpyridazin-3(2H)-one
5-Acetyl-2-ethyl-4-(2-naphthylamino)-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-6-phenyl-4-([3-(trifluoromethoxy)phenyl]amino)pyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-6-phenyl-4-([2-(trifluoromethyl)phenyl]amino)pyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(2,5-dimethoxyphenyl)amino]-6-phenylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-[(2-fluoro-3-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(2,3-dichlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(5-chloro-2-methoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(5-fluoro-2-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

Methyl 4-({5-acetyl-2-ethyl-6-[4-(methylthio)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoate

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one

4-({5-Acetyl-2-ethyl-6-[4-(methylthio)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoic acid

5-Acetyl-2-ethyl-6-[4-(methylthio)phenyl]-4-(1-naphthylamino)pyridazin-3(2*H*)-one

5-Butyryl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one

2-Ethyl-5-(2-ethylbutanoyl)-4-[(3-fluorophenyl)amino]-6-[4-(methylthio)phenyl]pyridazin-3(2*H*)-one

2-Ethyl-5-(2-ethylbutanoyl)-6-[4-(methylthio)phenyl]-4-(naphth-1-ylamino)pyridazin-3(2*H*)-one

Methyl 4-({5-acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-3-oxo-2,3-dihydropyrida-zin-4-yl}amino)benzoate

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-(1-naphthylamino)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(3-nitrophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(2-methoxyphenyl)amino]pyridazin-3(2H)-one

5-Acetyl-2-ethyl-6-[4-(methylsulphinyl)phenyl]-4-[(3-methoxyphenyl)amino]pyridazin-3(2H)-one

5-Acetyl-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-ethyl-4-(1-naphthylamino)pyridazin-3(2*H*)-one

5-Acetyl-2-methyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-benzyl-4-[(3,5-difluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-benzyl-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-benzyl-4-[(3-chlorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-(cyclopropylmethyl)-4-(1-naphthylamino)-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-(cyclopropylmethyl)-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-(1-naphthylamino)-6-phenyl-2-pyridin-4-ylmethylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3-fluorophenyl)amino]-6-phenyl-2-pyridin-4-ylmethylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(3-methylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid
2-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid
5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(3,4-dimethoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-(1,1'-biphenyl-4-ylamino)-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-6-phenyl-4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)pyridazin-3(2*H*)-one
5-acetyl-4-{[3-(cyclopentyloxy)-4-methoxyphenyl]amino}-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[*N*-methyl-*N*-phenylamino]-6-phenylpyridazin-3(2H)-one
5-Acetyl-4-(1,3-benzodioxol-5-ylamino)-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(4-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(4-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-4-[(4-bromophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-6-phenyl-4-{[3-(trifluoromethyl)phenyl]amino}pyridazin-3(2*H*)-one
5-Acetyl-4-[(3-chloro-4-methoxyphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one
5-Acetyl-2-ethyl-4-[(3-hydroxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one
3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid
5-Acetyl-2-ethyl-4-[(2-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
4-(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydro-pyridazin-4-ylamino)-benzoic acid ethyl ester
5-Acetyl-2-ethyl-4-[(4-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one
2-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-4-fluorobenzoic acid
3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-2-hydroxybenzoic acid

5-Acetyl-2-ethyl-4-[(3-hydroxy-4-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzamide

5-Acetyl-2-ethyl-4-{[3-(methylthio)phenyl]amino}-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-methoxyphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}acetic acid

5-Acetyl-4-[4-(*tert*-butylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzenesulphonamide

4-{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}-4-oxobutanoic acid

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]-*N*-butylbenzenesulphonamide

5-Acetyl-2-ethyl-4-[(1-oxo-2,3-dihydro-1H-inden-5-yl)amino]-6-phenylpyridazin-3(2H)-one

N-{4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]phenyl}acetamide

4-[5-Acetyl-6-(3-chlorophenyl)-2-ethyl-3-oxo-2,3-dihydropyridazin-4-ylamino]benzoic acid

5-Acetyl-6-(3-chlorophenyl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2*H*)-one

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(4-fluorophenyl)pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-(3-fluorophenyl)pyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(3-nitrophenyl)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-(3-nitrophenyl)pyridazin-3(2H)-one

4-{[5-Acetyl-2-ethyl-6-(3-nitrophenyl)-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzoic acid

5-Acetyl-4-[(3-bromophenyl)amino]-2-ethyl-6-(3-nitrophenyl)pyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-(naphthalen-1-ylamino)-6-(3-nitrophenyl)pyridazin-3(2H)-one

5-Butyryl-4-[(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-6-phenyl-2-propylpyridazin-3(2*H*)-one

5-Acetyl-2-butyl-4-[(3-chlorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-bromophenyl)amino]-2-butyl-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[*N*-(3,5-dichlorophenyl)-*N*-(3-fluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[bis(3-fluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[bis(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-[bis(3-methylsulphanylphenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[bis(3-acetylphenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[bis-(3,5-dichlorophenyl)amino]-2-ethyl-6-phenyl-2*H*-pyridazin-3-one

methyl 4-{*N*-(5-acetyl-2-ethyl-6-(4-methylsulphinylphenyl)-3-oxo-2,3-dihydropyri-dazin-4-yl)-*N*-[4-(methoxycarbonyl)phenyl]amino}benzoate

5-Acetyl-2-(cyclopropylmethyl)-4-[(3,5-difluorophenyl)amino]-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(3-fluorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2H)-one

4-[(5-Acetyl-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

5-Acetyl-4-[(3,5-dichlorophenyl)amino]-2,6-diphenylpyridazin-3(2H)-one

5-Acetyl-4-[(3-fluorophenyl)amino]-2,6-diphenylpyridazin-3(2H)-one

5-Acetyl-4-(1-naphthylamino)-2,6-diphenylpyridazin-3(2H)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2,6-diphenylpyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2,6-diphenylpyridazin-3(2H)-one

5-Benzoyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-methylpyridazin-3(2H)-one

5-[(3-Chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carbaldehyde

Methyl 5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylate

5-Acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-[2-(dimethylamino)ethyl]-6-phenylpyridazin-3(2H)-one

5-Acetyl-2-cyclobutyl-4-[(3,5-dichlorophenyl)amino]-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)(2-hydroxyethyl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

N-(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)-N-(3-chlorophenyl)urea

4-[(3-Chlorophenyl)amino]-5-[(dimethylamino)acetyl]-2-ethyl-6-phenylpyridazin-3(2H)-one

4-{[2-Ethyl-5-(methoxyacetyl)-6-phenyl-3-oxo-2,3-dihydropyridazin-4-yl]amino}benzoic acid

5-[(3-Cyanophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxamide

5-[(3-Cyanophenyl)amino]-1-ethyl-6-oxo-3-phenyl-1,6-dihydropyridazine-4-carboxylic acid

3-{4-Acetyl-5-[(3,5-difluorophenyl)amino]-1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl}benzoic acid

3-{4-Acetyl-5-[(3,5-difluorophenyl)amino]-1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile

N-(3-{4-Acetyl-5-[(3,5-difluorophenyl)amino]-1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl}phenyl)urea

5-Acetyl-4-[(3-chlorophenyl)amino]-6-phenylpyridazin-3(2H)-one

12. A compound according to claim 11 which is one of:

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-phenylpyridazin-3(2H)-one

5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

4-({5-Acetyl-2-ethyl-6-[4-(methylthio)phenyl]-3-oxo-2,3-dihydropyridazin-4-yl}amino)benzoic acid

5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-[4-(methylsulphinyl)phenyl]pyridazin-3(2*H*)-one

5-Acetyl-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

5-Acetyl-4-[(3,5-difluorophenyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-2-(cyclopropylmethyl)-4-[(3-fluorophenyl)amino]-6-phenylpyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-phenylpyridazin-3(2*H*)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-phenylpyridazin-3(2*H*)-one

3-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

4-[5-Acetyl-6-(3-chlorophenyl)-2-ethyl-3-oxo-2,3-dihydropyridazin-4-ylamino]benzoic acid

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2*H*)-one

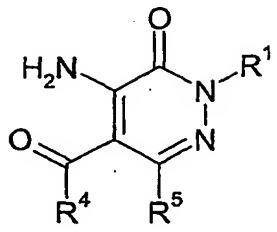
5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-(3-fluorophenyl)pyridazin-3(2*H*)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2*H*)-one

5-Acetyl-2-ethyl-4-(naphthalen-1-ylamino)-6-(3-nitrophenyl)pyridazin-3(2*H*)-one

5-Acetyl-2-(cyclopropylmethyl)-4-[(3,5-difluorophenyl)amino]-6-phenylpyridazin-3(2H)-one

13. A process for producing a compound of formula (I), as defined in any one of the preceding claims, and wherein R^2 is H, which process comprises reacting the corresponding 4-aminopyridazin-3(2*H*)-one derivative (II)



(II)

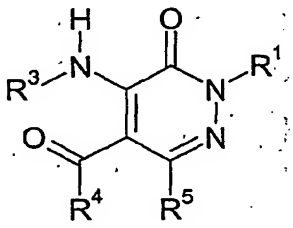
wherein R^1, R^4 and R^5 are as defined in any one of claims 1 to 3 and 7 to 10 and the corresponding boronic acid (IIIa)

$$R^3\text{-}B(OH)_2$$

(IIIa)

wherein R^3 is as defined in claims 1 and 6.

14. A process for producing a compound of formula (I), as defined in any one of claims 1 to 12, and wherein R^2 is aryl or substituted aryl, which process comprises reacting the corresponding 4-aminopyridazin-3(2*H*)-one derivative (IV):



(IV)

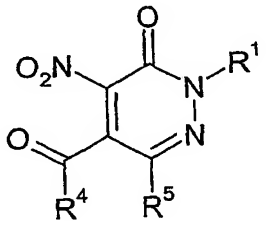
wherein R^1, R^3, R^4 and R^5 are as defined in any one of claims 1 to 3 and 6 to 10 and the corresponding boronic acid (IIIb)

$$R^2\text{-}B(OH)_2$$

(IIIb)

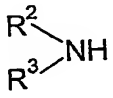
wherein R^2 is an aryl or substituted aryl group.

15. A process for producing a compound of formula (I), as defined in any one of claims 1 to 12, which process comprises reacting the corresponding 4-nitropyridazin-3(2*H*)-one derivative (V):



(V)

wherein R^1, R^4 and R^5 are as defined in any one of claims 1 to 3 and 7 to 10 and the corresponding amine (VI)



(VI)

wherein R^2 and R^3 are as defined in any one of claims 1 and 4 to 6.

16. A compound according to any one of claims 1 to 12 for the treatment of a pathological condition or disease susceptible to amelioration by inhibition of phosphodiesterase 4.

17. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 12 in admixture with a pharmaceutically acceptable carrier or diluent.

18. Use of a compound as defined in any one of claims 1 to 12 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible to amelioration by inhibition of phosphodiesterase 4.

19. Use according to claim 18 wherein the pathological condition is asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

20. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by inhibition of phosphodiesterase 4, which comprises administering to said subject an effective amount of a compound as defined in any one of claims 1 to 12.

5

21. A method according to claim 20 wherein the pathological condition is asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05056

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D237/22 C07D401/06 C07D405/12 A61K31/501 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DAL PIAZ, VITTORIO ET AL: "5-Acyl-6-aryl-4-nitro-3(2H)pyridazinones and related 4-amino compounds: synthesis and pharmacological evaluation" JOURNAL OF PHARMACEUTICAL SCIENCES (1991), 80(4), 341-8, XP002221780 compound 4g	1
A	WO 01 94319 A (BYK GULDEN LOMBERG CHEM FAB ;STERK GEERT (NL); BYK NEDERLAND BV (N) 13 December 2001 (2001-12-13) abstract	1,16-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2003	02/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/05056

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20,21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/05056

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0194319 A	13-12-2001	AU	6233201 A	17-12-2001
		BR	0111440 A	03-06-2003
		CA	2411351 A1	13-12-2001
		CZ	20023997 A3	14-05-2003
		WO	0194319 A1	13-12-2001
		EP	1296956 A1	02-04-2003
		NO	20025811 A	04-02-2003

1/1 *PLUSPAT - Comprehensive Worldwide Patents database*

Titles

Title (B1) PROCESS FOR PREPARING NOVEL ALKYLAMIDES OF 2-ANILINONICOTINIC ACIDS

Publication information

Patent Number *PL205246 A1 19791105 [PL-205246]*
Publication Stage *(A1) Application laid open*
Patent Number 2 *PL114780 B1 19810228 [PL-114780]*
Publication Stage 2 *(B1) Patent*
Priority Details *PL20524678 19780310 [1978PL-0205246]*
Application Data *PL20524678 19780310 [1978PL-0205246]*

Patent assignee

Patent assignee *(A1) INST PRZEMYSLU FARMACEUTIC (PL)*

Inventor(s)

Inventor *(A1) KRZYWOSINSKI LESZEK; KUSNIEREK BARBARA; PASZKOWSKA-REYNIER TERESA; BOGDAL MARIA; ERNEST*

Priority information

Priority Details *PL20524678 19780310 [1978PL-0205246]*

Application information

Application Data *PL20524678 19780310 [1978PL-0205246]*

Classification Codes

International Class. *(A1) C07D*

Other information

ICAA *C07D-213/82 [2006-01 A - I R M EP]; C07D-401/12 [2006-01 A - I R M EP]; C07D-413/12 [2006-01 A - I R M EP]*
ICCA *C07D [2006 S - I R M EP]; C07D-213/00 [2006 C - I R M EP]; C07D-401/00 [2006 C - I R M EP]; C07D-413/00 [2006 C - I R*